Journal of

CHRONIC DISEASES

VOL. 4 DECEMBER, 1956 NO. 6

Original Communications

TUBERCULOUS PERICARDITIS AMONG VETERANS

HEINZ BAUER, M.D.,* MORTON ROBINS, B.S., M.S.P.H.,** ROSE SACHS, B.A.,*** AND MARTIN M. CUMMINGS, M.D.,****

EMORY UNIVERSITY, GA.

(Received for publication July 25, 1956.)

TUBERCULOUS pericarditis is an uncommon form of tuberculosis characterized by a wide range of clinical and pathologic manifestations. The literature on the subject comprises relatively small series of cases collected in different ways from patient populations of varying composition. The findings of these studies are, therefore, often inconsistent and difficult to correlate. The present study of patients treated for tuberculous pericarditis by the Veterans Administration was undertaken to observe the effects of current therapy on the natural history of the disease, to provide additional clinical information, and to evaluate the relationships of age and race to incidence and prognosis of the disorder. This report differs from other series in that the cases are drawn from the entire U. S. veteran population whose size and demographic characteristics are known. Moreover, all cases occurred during a relatively short period of time and were followed for at least three years after clinical onset.

Presented at the 15th Veterans Administration-Army-Navy Conference on the Chemotherapy of Tuberculosis, St. Louis, Missouri, February 6-9, 1956, and at the Annual Meeting of the National Tuberculosis Association, New York City, May 20-25, 1956.

*Associate, Department of Pathology, Emory University School of Medicine.

**Chief, Biometrics and Evaluation Division, Department of Medicine and Surgery, Veterans Administration, Washington, D. C.

***Statistician, Biometrics and Evaluation Division, Department of Medicine and Surgery, Veterans Administration, Washington, D. C.

****Director, Research Service, Department of Medicine and Surgery, Veterans Administration, Washington, D. C.

SELECTION OF CASES

One million patients were discharged from the Veterans Administration hospital system during the 30 months' period, January, 1950, through June, 1952; 69 cases of tuberculous pericarditis were identified in the diagnostic cross-index file maintained centrally on a 50 per cent random sample of these patients. A specially designed abstract form, shown in the Appendix, was systematically completed by one of us (H. B.) upon review of the clinical records for each study case. Follow-up information pertaining to subsequent hospitalization, clinical status, and mortality was obtained from a review of each veteran's claim folder.

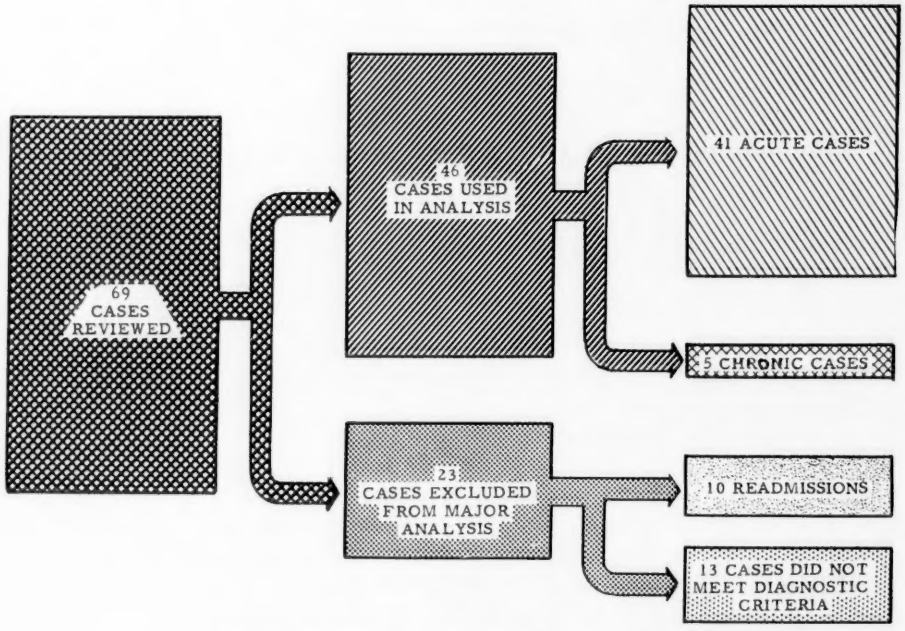


Fig. 1—Selection of cases of tuberculous pericarditis.

Thus, a fairly complete medical history was available on each patient, extending from three to nine years after the onset of pericarditis. The criteria established for the study were similar to those used by Falk and Ebert.[1] In fact, 3 of their 21 patients are also included in this analysis. The cases included in this study were then classified as to proof of tuberculous etiology in one of the following categories:

Class I. *Proved tuberculous etiology* on the basis of bacteriologic or histologic examination or both.

Class II. *Probable tuberculous etiology* in the presence of concurrent extrapericardial tuberculosis.

Class III. *Presumptive tuberculous etiology* without concurrent extrapericardial tuberculosis on the basis of clinical picture, positive tuberculin skin test, and, in some cases, a dramatic response to streptomycin after other therapy produced no response.

The final grouping of the 69 cases is shown in Fig. 1. Twenty-three did not meet the clinical or statistical criteria set up for this study. Ten of these, while diagnostically suitable, were considered to present a biased group in the appraisal of the incidence and natural history of the disease because they were not "initial hospital admissions" but were discharged during the study period following readmission for previously diagnosed tuberculous pericarditis.

The reasons for excluding the other 13 patients are shown in Table I. Six cases did not conform to our diagnostic standards. These patients have been followed for at least four years and, by January, 1956, had not developed any form of tuberculosis. Two patients had no clinical manifestations and tuberculous pericarditis was an incidental finding at autopsy. In 3 others, pericardial involvement occurred as a complication of thoracic surgery. In the last 2 patients, the clinical picture was consistent with tuberculous pericarditis but autopsy disclosed carcinomatosis in one and nontuberculous polyserositis in the other.

TABLE I. REASONS FOR EXCLUSION OF CASES NOT MEETING DIAGNOSTIC CRITERIA OF STUDY

REASON FOR EXCLUSION	NUMBER OF CASES
Total cases	13
Insufficient clinical evidence of tuberculous pericarditis*	6
Pericarditis a complication of thoracic surgery	3
Autopsy diagnosis of tuberculous pericarditis with no clinical manifestations	2
Clinical diagnosis of tuberculous pericarditis disproved at autopsy	2

*These patients were followed for four years without evidence of tuberculosis.

Forty-six patients were considered suitable for study. Forty-one of these cases were acute and 5 were chronic (constrictive) tuberculous pericarditis at the time of first observation. The 5 chronic cases were not included in the analysis of signs and symptoms, laboratory findings, and the evaluation of the effect of chemotherapy on the course of the disease.

In 16 of the 41 patients with acute tuberculous pericarditis (Fig. 2) the etiology was proved (Class I). Twelve of these were proved bacteriologically by culture or guinea pig inoculation (2 of these 12 were also confirmed histologically), and 4 of them by histologic study only. Twenty patients fell into Class II and 5 into Class III. Of the latter, 2 showed a dramatic response to streptomycin and another patient in this group developed tuberculous lymphadenitis eleven months after treatment for tuberculous pericarditis.

INCIDENCE

According to a recent review by Anderson,[2] tuberculous pericarditis is found in 0.4 to 1.0 per cent of all autopsies. Wolfe[3] reported it in 0.48 per cent of 26,389 consecutive necropsies and Griffith and Wallace[4] in 0.41 per cent of a similar large series. Among all types of pericarditis, tuberculosis occurs in 8 per cent,[5] 8.4 per cent,[6] and 10 per cent.[7] Diefenbach[8] reported that tuberculous pericarditis occurs at one time or another in 3 per cent of all patients with tuber-

culosis. During the period of this study, January, 1950, through June, 1952, it was found that tuberculous pericarditis was diagnosed in about 0.2 per cent of all tuberculous patients discharged from Veterans Administration hospitals.

No report has been found, however, of the incidence of tuberculous pericarditis in terms of the number of new cases occurring during a specified time period in a population of known size. The present review of a sample of tuberculous pericarditis patients discharged from Veterans Administration hospitals

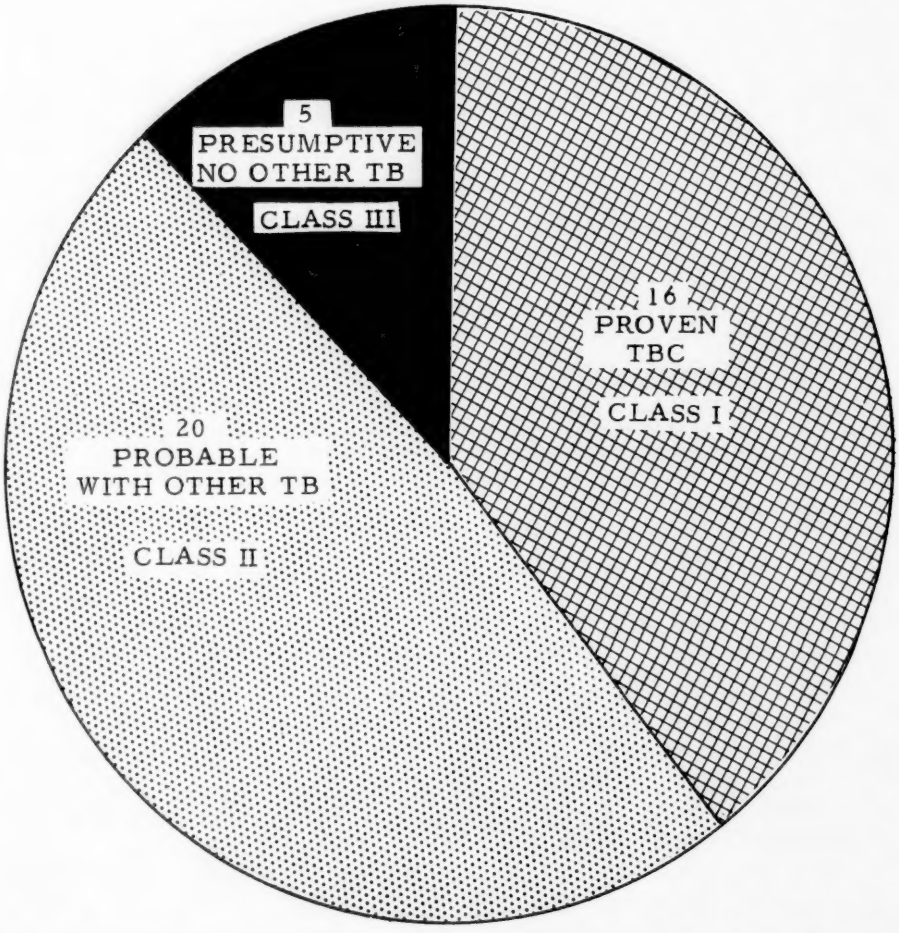


Fig. 2.—Distribution of 41 acute cases of tuberculous pericarditis according to diagnostic criteria.

permits an estimate to be made of the annual incidence of the disease among the more than 19,000,000 male veterans in the United States. The following conditions are assumed in making this estimate: (1) that the number of veterans discharged annually following their *initial* treatment for tuberculous pericarditis in VA hospitals approximates the number of veterans in whom the onset of this condition occurred during the year and who will eventually obtain hospitalization

in a VA hospital; and (2) that approximately 80 per cent of all veterans requiring hospital care for tuberculous pericarditis obtain such care in VA hospitals.

We observed 46 cases in a 50 per cent sample of patients discharged from VA hospitals in a two and one-half-year period. From this, it is estimated that there were about 37 patients with tuberculous pericarditis discharged each year. Since we believe that this number represents approximately 80 per cent of all veterans who required hospitalization during each year for tuberculous pericarditis, it is estimated that there were about 46 veterans each year who had an initial attack of tuberculous pericarditis. Inasmuch as our estimate of annual incidence is the same as the total number of cases observed in our sample of discharged patients, the latter group has been used to represent the distribution by age and race of cases which had their onset during a given year. The annual incidence rate of tuberculous pericarditis among U. S. veterans during 1950 is therefore estimated to be about 2.4 per million veterans.

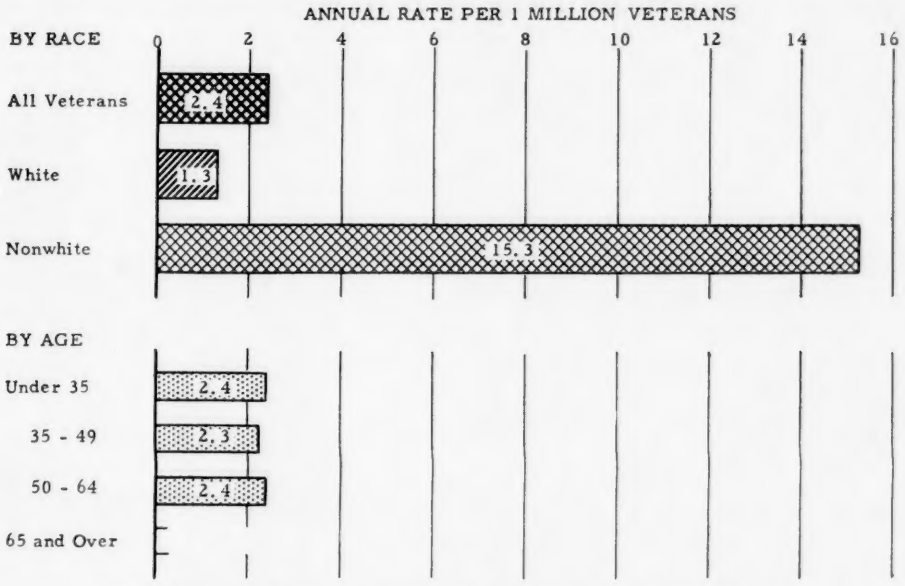


Fig. 3.—Estimated annual incidence rates of tuberculous pericarditis among U. S. veterans by race and age.

The true incidence of tuberculous pericarditis among the population in general is probably higher than any of the figures indicate. The disease may be overshadowed by pulmonary or other forms of tuberculosis. Cases may be mild and misdiagnosed as acute idiopathic pericarditis. It must also be considered that healing probably occurs even in untreated cases and that tuberculous pericarditis may go on to nonspecific pericardial fibrosis without being recognized. Anderson[2] mentions three patients with bacteriologically proved tuberculous pericardial effusion whose pericardial tissue removed surgically disclosed no histologic evidence of tuberculosis.

Race.—The annual incidence rates by race and age are shown in Fig. 3. A more detailed breakdown is given in Table II.

The high number of Negroes affected by tuberculous pericarditis has long been stressed. Harvey and Whitehill[9] reported 72 per cent Negroes in their series from the Johns Hopkins Hospital. In Goyette, Overholt, and Rappaport's[10] series from the U. S. Army, 59 per cent were Negroes. In Falk and Ebert's[1] group of selected U. S. veterans, 50 per cent belonged to the Negro race. However, only for populations such as the U. S. Armed Forces and veterans, whose racial composition is known, can the relative incidence rates among whites and nonwhites be validly compared. In our series of 46 patients, 23 were white and 23 were nonwhite. (One Mexican is included among the whites and one American Indian among the nonwhites.) These frequencies were related to the distribution by race of the total veteran population of 19 million from which these patients were drawn. The incidence rate among nonwhite veterans (15.3 per million) is estimated to be about 12 times as great as that among white veterans (1.3 per million). It is of interest to note that Goyette, Overholt, and Rappaport[10] also found a race differential of about 12 to 1 among Army personnel.

TABLE II. ESTIMATED ANNUAL INCIDENCE RATE OF TUBERCULOUS PERICARDITIS AMONG U. S. VETERANS, BY AGE AND RACE

(Based on a 50 per cent sample of VA patients discharged January, 1950, to June, 1952.)

AGE AND RACE	ESTIMATED U. S. VETERAN POPULATION AS OF 7/1/50 (IN THOUSANDS)	ESTIMATED NO. OF CASES PER ANNUM*	ESTIMATED RATE PER MILLION VETERANS PER ANNUM
Total, all ages	19,100	46	2.4
Under 35	11,300	28	2.4
35–49	3,900	9	2.3
50–64	3,700	9	2.4
65 and over	200	—	—
White, all ages	17,600	23	1.3
Nonwhite, all ages	1,500	23	15.3

*The number of cases per annum is estimated as equal to the number of initial admissions of patients with tuberculous pericarditis observed in the 50 per cent sample of patients discharged from VA hospitals during the 30-month period, January, 1950, to June, 1952.

Age.—Cases of tuberculous pericarditis have been reported among children[11] and adults of all ages. In our series, 28 of the 46 patients were under 35 years of age; 9 were between 35 and 49; 9 were between 50 and 64; and no patient was 65 years or older. Since the veteran population is primarily composed of young adults, however, the numerical distribution of the observed cases by age does not necessarily reflect any age differential in the incidence rate of pericardial tuberculosis. In fact, Table II and Fig. 3 show that the incidence rate was approximately 2.4 cases per million veterans in each of the three age groups. Since the number of veterans aged 65 and over was only 200,000, no cases could be expected statistically in this age group even if the incidence rate among these older veterans was the same as that observed among the younger veterans. The effect of age on prognosis will be discussed later.

Sex.—Tuberculous pericarditis is considered to be predominantly a disease of males. The literature reports series of cases in which between 70 and 90 per

cent were males.[9,12-14] Despite the fact that all of our patients were men, this finding cannot be taken as indicative of a sex differential in incidence rates among veterans. Even if the annual incidence rate among female veterans were as high as that estimated for male veterans, no cases could statistically be expected in our series since there were only 350,000 women in the U. S. veteran population in 1950.

PATHOGENESIS

The essentials of the pathogenesis of tuberculous pericarditis are those of any tuberculous infection and will not be discussed here. In general, the organisms may reach the pericardium in the course of hematogenous dissemination, by retrograde spread from mediastinal lymph nodes, through rupture of a caseous mediastinal lymph node or of an adjacent pulmonary focus. Not infrequently tuberculous pericarditis may be the first clinical manifestation of tuberculosis. In our series of 41 acute cases, 31 had some form of clinically active (and 2 had inactive) extrapericardial tuberculosis at the time of onset of pericardial disease; while in 8 patients the disease was clinically "primary," i.e., limited to the pericardium when first observed. Of these 8 patients, 5 developed other forms of tuberculosis later and only 3 showed no evidence of extrapericardial tuberculosis although they were followed for at least five years after the onset of pericarditis.

Tuberculosis of mediastinal lymph nodes was observed in 2 of our acute cases at the time of onset of pericarditis and 5 other patients developed mediastinal adenopathy later. Rupture of a caseous node into the pericardial sac was the probable cause of pericarditis in one of our patients. Anderson[2] found such a node inseparably attached to a fibrotic pericardium in which no active tuberculosis could be demonstrated histologically. In Todd's[11] patients, an adjacent caseous lung focus in one and a caseous mediastinal lymph node in another patient were found at autopsy but rupture into the pericardial cavity could not be proved. Fistulous tracts[14] and firmly attached active lung and lymph node foci[15] are encountered in other series. This route appears to be one of the less common pathways of infection, however.

The majority of patients with acute tuberculous pericarditis have other concurrent manifestations of tuberculosis or are apt to develop them later. It is significant that Diefenbach[8] was unable to find a single valid published case in which the pericardium was the only site of tuberculosis at autopsy. The patients with so-called primary tuberculous pericarditis[13,16] reported in the literature all showed extrapericardial disease at the time of death.

PATHOLOGY

The pathology of tuberculous pericarditis is well known and has recently been reviewed by Anderson.[2] The characteristics of the pericardial fluid in this disease will be discussed later. Since the advent of chemotherapy, one has to keep in mind that walled-off caseous pericardial abscesses may persist for a long time and occasionally complicate pericardectomy.[17]

SIGNS AND SYMPTOMS

Onset.—The onset of tuberculous pericarditis is often insidious compared with that of other types of pericarditis. This fact has been pointed out by many

observers.[18,19] Symptoms may be severe enough for the patient to seek early medical care, however. In Wood's[18] series, 15 per cent of his patients were seen within one week after the appearance of symptoms. Fifteen of our 41 cases were recognized early since these patients were already hospitalized for other forms of tuberculosis, and 8 additional patients were seen within less than two weeks after onset. Considering the many factors which play a part in the early recognition of tuberculous pericarditis by the physician or the patient, the mode of onset is of little significance in differentiating between tuberculous and other forms of pericarditis.

TABLE III. OBSERVATION OF 41 CASES OF ACUTE TUBERCULOUS PERICARDITIS. RELATIONSHIP BETWEEN DIAGNOSTIC SYMPTOMS AND SIGNS AT FIRST OBSERVATION AND INTERVAL BETWEEN ONSET AND FIRST OBSERVATION

(Based on a 50 per cent sample of VA patients discharged January, 1950, to June, 1952.)

DIAGNOSTIC SYMPTOMS AND SIGNS AT FIRST OBSERVATION	INTERVAL BETWEEN ONSET AND FIRST OBSERVATION					
	LESS THAN 2 WEEKS OR DIAGNOSED WHILE IN HOSPITAL		MORE THAN 2 WEEKS		TOTAL CASES	
	NUMBER	%	NUMBER	%	NUMBER	%
Total cases	23	100	18	100	41	100
Enlarged heart	23	100	18	100	41	100
Fever	20	87	15	83	35	85
Chest pain	19	83	7	39	26	63
Dyspnea	15	65	18	100	33	80
Tachycardia	13	56	12	67	25	61
Friction rub	13	56	9	50	22	54
Pleural effusion	11	48	14	78	25	61
Distant heart sounds	11	48	11	61	22	54
Feeble apex beat	9	38	10	56	19	46
Enlarged liver	9	38	13	72	22	54
Paradoxical pulse	6	26	10	56	16	39
Cervical venous distention	5	22	7	39	12	29
Edema	2	9	8	44	10	24
Ascites	—	0	8	44	8	20
Auricular fibrillation	—	0	2	11	2	5

Clinical Observations.—The clinical findings at time of first observation in a Veterans Administration hospital are shown in Table III. Enlargement of the cardiac silhouette on physical or roentgenologic examination, dyspnea, and fever were observed in almost all cases. About half the patients also had tachycardia, friction rub, and distant heart sounds on auscultation. The importance of paradoxic pulse,[20] the significance of a pericardial friction rub,[21] and the diagnosis of pericardial disease by physical examination[22] have been clearly stated by others and do not need to be repeated here. With regard to other findings, a distinct difference was noted between those patients observed within two weeks after

clinical onset and those seen later during the course of their illness. While chest pain was a common symptom in the first group, it was uncommon among the patients of the second. On the other hand, clinical signs of impaired cardiac function such as hepatomegaly, paradoxic pulse, cervical venous distention, edema, and ascites were noted more frequently among the patients seen more than two weeks after the appearance of the symptoms.

LABORATORY FINDINGS

White blood cell count, differential white blood cell count, hemoglobin content of the blood, and urinalysis yielded no consistent results and were influenced by the patient's nutrition, age, and extrapericardial tuberculosis. The erythrocyte sedimentation rate was determined for 36 of the 41 acute cases and was elevated in all but 3 instances. Measurements of venous pressure were carried out in 30 of the 41 acute cases and 23 of these had values of 150 mm. of water or over. These venous pressure findings generally reflected the cardiovascular status of the patients.

Pericardial Fluid.—The character and composition of the pericardial fluid and the bacteriologic findings are shown in Table IV. No differences were noted

TABLE IV. SUMMARY OF PERICARDIAL FLUID OBSERVATIONS ON 41 PATIENTS WITH ACUTE TUBERCULOUS PERICARDITIS

(Based on a 50 per cent sample of VA patients discharged January, 1950, to June, 1952.)

ITEM		NO. OF CASES	
A. Use of Paracentesis and Results.—			
1. Total cases			41
Fluid obtained		23	
Fluid not obtained		18	
Unsuccessful tap		3	
Not aspirated		15	
B. Description of Pericardial Fluid.—			
1. Results of bacteriologic tests			23
Tubercle bacilli found		12	
Tubercle bacilli not found		10	
Not reported		1	
2. Character of fluid			23
Hemorrhagic		10	
Cloudy		7	
Serous		1	
Unknown		5	
3. Specific gravity			7
Average	1.021		
Range	1.017 - 1.026		
4. Protein			8
Average	4.2 Gm./100 c.c.		
Range	2.7 - 6.7 Gm./100 c.c.		

between those fluids which yielded *Mycobacterium tuberculosis* on smear, culture, or guinea pig inoculation and those which did not. Hemorrhagic effusion was the most common type, although other types were also observed. High specific gravity and high protein content were present whenever such determinations were done. Unfortunately, most aspirates were studied bacteriologically only. More than half of all the fluids were positive for *Myco. tuberculosis.* Many patients showed improvement in their cardiovascular status after pericardiocentesis and no complications followed the procedure.

Pleural Effusion.—Twenty-five of the 41 patients had pleural effusion at the time of initial examination and 6 others developed effusions later. Of the 31 pleural effusions observed, 9 were left-sided, 15 right-sided, and 7 were bilateral. Pleural fluid was aspirated in 16 patients and bacteriologic proof of a tuberculous etiology was obtained in 5 instances (37 per cent).

Electrocardiograms.—ECG tracings were taken of all patients and in all instances were abnormal since the presence of a normal electrocardiogram was considered a reason for the exclusion of cases from the study. The tracings showed the characteristics of pericarditis as recently reviewed by several authors.[1,2] In view of these previous studies no attempt was made to analyze and summarize the electrocardiograms of the patients in our series.

Roentgenography.—A routine chest roentgenogram was the only type of diagnostic radiologic evaluation used in our series. Enlargement of the cardiac shadow was evaluated by the cardiothoracic ratio. Resolution of the pericarditis either by healing or by transition into constrictive pericarditis was associated with a measurable decrease in the heart size in all but one case. These changes, therefore, are important follow-up observations. The importance of the roentgenogram in diagnosis will be further discussed later.

DIAGNOSIS

The most important diagnostic procedure in tuberculous pericarditis is undoubtedly the bacteriologic examination of the pericardial fluid. A tuberculous etiology was established with certainty in more than half of the patients from whom fluid was obtained. Similar rates of recovery of the organism are reported by others.[2,18] The dangers of pericardiocentesis should not be minimized although no complications occurred in our series. Kotte and McGuire[28] have recently polled a group of leading cardiologists and surgeons, each of whom reported having seen at least one death resulting from the procedure. However, Estes, Bishop, and McIntosh[29] in an unpublished report recently stated that danger of entering the myocardium while performing a pericardiocentesis was avoided in 40 cases when an electrocardiogram was used concomitantly. The possibility of complications does not outweigh diagnostic necessity if proper precautions are observed. The removal of excess pericardial fluid should never be regarded as a last resort for patients already in severe cardiac difficulties. Some patients have probably died for lack of this lifesaving measure.[2] Diagnostic pericardial biopsy has recently been used with good results.[22,23]

In cases with concurrent pleural effusion, the pleural fluid should also be aspirated, bacteriologically studied, and, if indicated, biopsy of the pleura may prove useful.[2,24-26] Although in some instances pleural effusion may be caused by the congestive heart failure resulting from the patient's pericarditis, there is no way of determining the etiology of the pleural fluid with certainty and it should be regarded as tuberculous until proved otherwise.

When the clinical picture suggests tuberculous pericarditis and there is no clinically manifest extrapericardial tuberculosis, such foci should be searched for by all available bacteriologic, roentgenologic, and other means. A tuberculin skin test is, of course, essential. Arrested extrapericardial tuberculosis does not rule out a tuberculous etiology of the patient's pericarditis.

Acute benign or idiopathic pericarditis often presents a difficult problem in differential diagnosis. In tuberculous pericarditis, the onset is usually gradual and pain is often mild,[27] whereas suddenly developing sharp pericardial pain appearing in an otherwise asymptomatic person suggests the idiopathic type. The latter is a self-limited disease and therefore the sense of well-being of the patient is disturbed only shortly before onset and returns to normal within a week or so. In untreated tuberculous pericarditis, patients are more apt to feel malaise for a much longer period of time before and after clinical onset of pain. The color, protein content, specific gravity, and cell count of the pericardial fluid are of little help in differentiating the two conditions. The recurrent course which idiopathic pericarditis sometimes takes is rare in tuberculous disease but may occur. Janovsky and his associates[22] have reported upon a patient with many recurrent bouts of pericarditis who, at pericardiectomy, showed tuberculous pericarditis.

Tumors of the pericardium, rheumatic fever, systemic lupus erythematosus, myocardial infarction, and other diseases can usually be differentiated from tuberculous pericarditis. However, Harrington[29] reported upon a patient with a history of rheumatic fever whose pericardium showed active tuberculosis histologically. Bouvrain and Pages-Darteville[14] mentioned a patient with polyarthritis who was also proved to have tuberculous pericarditis. Cytologic examination of the pericardial fluid may reveal the presence of malignant tumors. A purulent effusion is rare in tuberculous pericarditis but may occasionally be seen.[2] Routine as well as special media for *Myco. tuberculosis* should be used in such instances unless the etiology is clinically clear.

The importance of roentgenologic procedures as an aid in diagnosis and in following the patient's clinical course is obvious, although pericardial effusions of less than 200 to 300 c.c. may be missed on routine chest roentgenograms.[30,31] Re-examination after pericardiocentesis is often useful. Aside from gauging the decrease in the cardiac silhouette, the replacement of the removed fluid by air may outline the true size of the heart and the character of the pericardial surfaces. Furthermore, when the heart shadow becomes smaller, previously obscured tuberculous mediastinal lymph nodes may become visible.[32] Fluoroscopy is, of course, also useful. Barium swallow and angiocardiography have sometimes been employed.[8]

CHEMOTHERAPY AND MORTALITY

Most of our study cases received various regimens of streptomycin in combination with para-aminosalicylic acid. Five patients were treated with streptomycin alone and one patient was given streptomycin and isonicotinic hydrazide in combination. Only four patients received no chemotherapy. The effect of chemotherapy on survivorship is summarized in Table V. Twenty-nine of the 41 patients with acute tuberculous pericarditis received chemotherapy for more than two months, including 15 patients whose course of treatment extended over more than six months. Only 3 (about 10 per cent) of the 29 patients given prolonged chemotherapy died. Of 8 patients who received chemotherapy for less than two months, 5 died. Three of these died from cardiac disease while they were receiving chemotherapy; the remaining 2 patients died of miliary and disseminated tuberculosis after their pericarditis had clinically improved and no pericardial disease was found at autopsy. Thus, the high fatality rate among the group of patients treated for less than two months is somewhat deceptive, and cannot be interpreted as indicative of poor response to short-term chemotherapy. No definitive conclusions are possible as to the efficacy of more prolonged chemotherapy but considering the fact that the mortality in the pre-chemotherapy era ranged around 80 to 90 per cent,[9,14,18] it seems safe to conclude from our data and from other recent reports that the outlook for patients with tuberculous pericarditis will be vastly improved by the use of prolonged chemotherapy. The administration of isonicotinic hydrazide will undoubtedly further improve this favorable prognosis.

TABLE V. USE OF CHEMOTHERAPY AND OBSERVED SURVIVORSHIP* IN 41 CASES OF ACUTE TUBERCULOUS PERICARDITIS

(Based on a 50 per cent sample of VA patients discharged January, 1950, to June, 1952.)

SURVIVORSHIP	TOTAL	NO CHEMOTHERAPY	CHEMOTHERAPY	
			LESS THAN TWO MONTHS	TWO MONTHS OR MORE
Total patients	41	4	8	29
Alive	32	3	3	26
Died	9	1	5	3
Without circulatory failure	3	—	2	1
With circulatory failure	6	1	3	2

*All cases were followed for at least 3 years after onset.

The question of intrapericardial injection of streptomycin advocated and used by Tapie and his co-workers[34] probably has no advantages over the conventional route, particularly since the advent of isonicotinic hydrazide. Injection of streptokinase and streptodornase into the pericardial cavity to prevent formation of adhesions and subsequent constrictive pericarditis was used in 2 of our patients without significant effect. In one patient, the thickened pericardium was noted by x-ray studies to have thinned out markedly but the patient went on to develop constrictive pericarditis.

CAUSES OF DEATH

The mortality experience of our study cases is summarized numerically in Table VI and graphically (from analyses by the modified life table methodology) in Fig. 4. There were 9 deaths among the 41 patients with acute tuberculous

TABLE VI. SURVIVORSHIP IN 41 CASES OF ACUTE TUBERCULOUS PERICARDITIS FOLLOWED FOR AT LEAST THREE YEARS AFTER ONSET, ACCORDING TO AGE ON ONSET OF PERICARDITIS

(Based on a 50 per cent sample of VA patients discharged January, 1950, to June, 1952.)

SURVIVORSHIP	NUMBER OF CASES			%		
	TOTAL	UNDER 50	50 AND OVER	TOTAL	UNDER 50	50 AND OVER
Total cases	41	33	8	100	100	100
Alive	32	28	4	77	85	50
Died	9	5	4	23	15	50
Without circulatory failure	3*	2	1	8	6	13
With circulatory failure	6†	3	3	15	9	37

*Distribution of these 3 cases according to interval between onset and death: 1 case each in sixteenth, twenty-sixth, and sixty-first months.

†Distribution of these 6 cases according to interval between onset and death: 2 cases within 2 months; 1 case each in third, fourteenth, fifteenth, and thirty-first months.

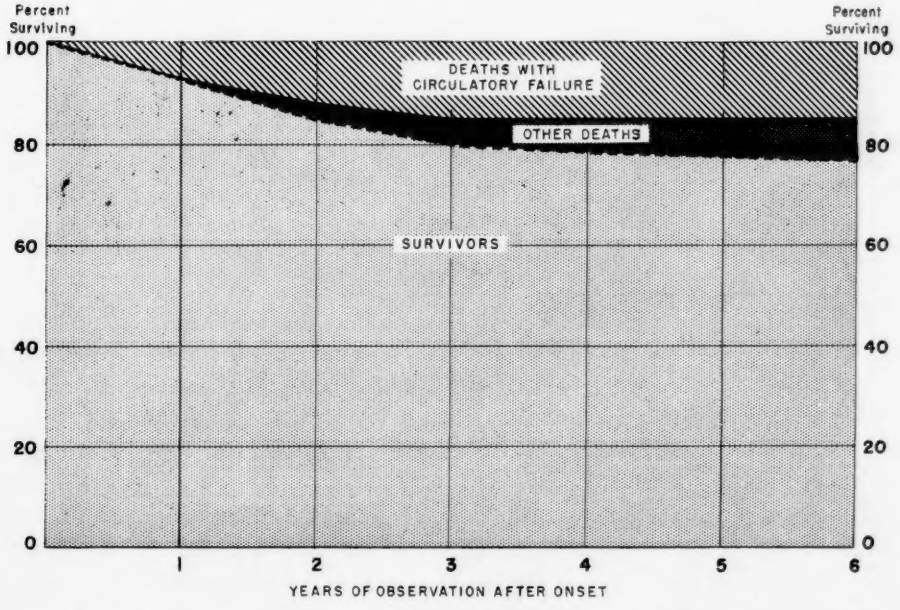


Fig. 4.—Estimated survivorship of acute tuberculous pericarditis over a six-year period following onset.

pericarditis. Eight patients died within three years and one patient five years after the clinical onset of pericarditis. In 3 of these 9 cases, death was primarily due to miliary, disseminated, or meningeal tuberculosis after pericardial disease had become clinically asymptomatic. The other 6 patients showed some circulatory difficulties and 5 of them had far-advanced extrapericardial tuberculosis as an important contributory cause of their demise. One patient died suddenly, probably of myocardial infarction, but no autopsy was performed. Our findings are in agreement with other reports stressing that widespread systemic tuberculosis is commonly found at the time of death in patients with tuberculous pericarditis.[9,14,34]

Age is an important factor in the prognosis of tuberculous pericarditis. The relationship of age to mortality and congestive heart failure is shown in Table VI. Half of our patients 50 years and older died while only 15 per cent of those below that age succumbed.

The presence of congestive heart failure is said to increase the mortality from tuberculous pericarditis. This held true in our series where 8 of the 9 deaths occurred in patients with clinical signs of circulatory failure prior to death. The high case fatality rate associated with circulatory failure was observed both in those under and those over 50 years of age. The various factors which may enter into the development of this complication could not be satisfactorily evaluated with the data at our disposal, but the occurrence of congestive heart failure should be regarded as a serious omen in patients with tuberculous pericarditis.

CONSTRICTIVE PERICARDITIS

Eleven (27 per cent) of the 41 patients with acute tuberculous pericarditis developed constrictive pericarditis during the period of observation, 8 of these after two months or more of chemotherapy. Six underwent pericardiectomy and all were alive and improved 2 to 5 years later. Three of the 5 patients who did not undergo operation died. Constrictive pericarditis was also observed in 11 additional cases which were not included in the 41 acute cases. This group is composed of the 5 patients with chronic constrictive pericarditis at the time of first VA observation, and 6 patients who developed constrictive pericarditis among the 10 cases excluded from this study because they were "readmission" cases. Nine of these patients eventually underwent pericardiectomy and only one died of intractable postoperative shock. Both patients who were not operated upon are dead.

Thus, of 22 patients with constrictive pericarditis, 15 had pericardiectomy with only one death while 5 of the 7 patients not operated upon have succumbed. Although some of the patients who were not operated upon were unsuitable for surgery for various reasons, the difference in mortality is so great that it is safe to conclude that patients with constrictive pericarditis who undergo pericardiectomy have a more favorable prognosis than those not so treated.

VOL.
4
956

SUMMARY

The present study of patients treated by the Veterans Administration for tuberculous pericarditis was undertaken to describe the effect of current therapeutics on the natural history of the disease and to provide additional facts on the clinical picture of the disease and its relative incidence according to age and race. It differs from previously reported series in that the cases occurred during a short time period and are drawn from the entire U. S. veteran population whose size and demographic characteristics are known. Moreover, survivorship data have been determined for the study cases for at least a three-year period subsequent to the onset of the clinical manifestations of the disease.

The major study findings are:

1. The annual incidence rate among U. S. veterans is estimated to be about 2.4 cases per million veterans. Based on the observed incidence rate, no cases would be expected among the 350,000 female veterans; none was reported in our series. The observed rate among nonwhite veterans (15.3) was about 12 times as great as that among white veterans (1.3) No appreciable differences were observed between the age-specific incidence rates among veterans between 20 and 65 years of age.

2. The most commonly observed clinical signs and symptoms were enlarged heart, dyspnea, and fever. The relative frequency of certain other significant clinical findings was associated with the time interval between presumed onset and first observation in a VA hospital. The 23 patients observed more than two weeks after onset were more frequently found to have clinical evidence of extension of cardiac pathology as manifested by such signs as edema, ascites, enlarged liver, and cervical venous distention. The predominant differential symptomatology observed among the remaining 18 cases examined within two weeks of presumed onset of symptoms was chest pain and the relative absence of signs of cardiac impairment.

3. Nine deaths were observed among the 41 acute cases followed over a period of more than three years after onset of their disease. In 3 of the 9 deaths, the cause was unrelated to the tuberculous pericarditis which had become essentially asymptomatic, but was attributed to extensive extrapericardial tuberculosis; 2 patients had miliary or disseminated tuberculosis and one had meningeal tuberculosis. The other 6 deaths could have been related to impaired cardiac function.

4. Only 4 of the 41 acute cases did not receive chemotherapy. Of the 37 patients who received some form of chemotherapy, 29 had more than two months of treatment and 8 had a shorter course. Death interrupted chemotherapy in 3 cases. Since case fatality ratios of 85 per cent have been reported in the literature in the prechemotherapy era, the occurrence of only 8 deaths among the 37 study patients given chemotherapy indicates the value of the antibiotic treatment used.

5. Of 22 patients with constrictive pericarditis, 15 underwent pericardiectomy with only one death, while 5 of the patients not operated upon succumbed. It appears that patients with constrictive pericarditis treated surgically have a better prognosis than those treated conservatively.

APPENDIX

CASE REPORT FOR TUBERCULOUS PERICARDITIS | Reports Control Symbol

1. Reporting Hospital	2. Patient's Name	3. Register No.	4. Case No.

5. Date of Birth (Mo., Day, Yr.)	6. Sex ☐M ☐F	7. Race ☐W ☐N ☐O	8. Date of Onset of Pericarditis	9. Date of Admission

10. *Major Diagnoses or Complications at Time of Diag. of Tuberculous Pericarditis*

a. ☐ Pulm. Tbc: ☐ Active ☐ Arr. ☐ Inact.
b. ☐ Pleurisy c Eff.: Proven Tbc: ☐ Yes ☐ No
c. ☐ Tbc of pleura
d. ☐ Tbc of peritoneum
e. ☐ Miliary Tbc (Specify sites): _____
f. ☐ Other (Specify): _____

Date of Onset	For Coding Purposes
	A.
	B.
	C.
	D.
	E.
	F.

11. Diagnostic Signs	Absent or Normal	Present or Abnormal	Unknown	Remarks	For Coding Purposes
a. Fever (range & dur.)				(R&D) _____	G.
b. Pulse (range)				(R) _____	H.
c. Paradox				☐ Right ☐ Left ☐ Bilat.	I.
d. Pleural effusion					J.
e. Edema					K.
f. Ascites					L.
g. Friction rub					M.
h. Chest pain					N.
i. Heart size					O.
j. Dyspnea					P.
k. Feeble apex beat					Q.
l. Dist. heart sounds					R.
m. Auric. fibrill.					S.
n. Enlarged liver					T.
o. Cerv. venous dist.					U.
p. Venous pressure _____ cm. H_2O					V.
q. Sedimentation rate: _____					W.
r. Blood pressure: Systolic _____ Diastolic _____					X.

VA Form 10–8-69 9-62

CASE REPORT FOR TUBERCULOUS PERICARDITIS (page 2) | CASE NO.

12. Laboratory Tests for Diagnosis	Smear	Cult. or G.P.	Amount (c.c.)	Color	S. G.	Prot.	Sug.	For Coding Purposes
a. Sputum			XXXX	XXXX	XXXX	XXXX	XXXX	1.
b. Urine			XXXX	XXXX			XXXX	
c. Pleural fluid							XXXX	2.
d. Pericardial fluid							XXXX	
e. Ascitic fluid							XXXX	3.
f. Pericardial tissue			XXXX	XXXX	XXXX	XXXX	XXXX	
g. Blood: WBC RBC Diff.								4.
h. OT or PPD: Date Reaction								5.
Changes PTA or AA								6.
i. Other significant findings:								7.
								8.

13. Chemotherapy: Previous Rx: None Yes (Drug and Dates in Remarks Sect.) 9.

Drug	Dosage	Freq.	Date Begun	Date Ended	Sgns. AFB to Drug		
					Prior to Rx	End of Rx	
a.							10.
b.							11.
c.							12.
							13.
							14.

14. Bacteriology – After Start of Rx

Specimen	1st month			2nd month			3rd month		
	Date	Sm.	Cult. or G.P.	Date	Sm.	Cult. or G.P.	Date	Sm.	Cult. or G.P.
a.									
b.									

15. Surgery	Date	Surg. Complications	Result
a.			
b.			
c.			

VOL.
4
1956

CASE REPORT FOR TUBERCULOUS PERICARDITIS (page 2A) | CASE NO.

15. Laboratory Tests – Post-Rx or Postdiagnosis if no Rx given

Specimen	1st month		2nd month		3rd month		4th month		5th month		6th month	
	SM	Cult. or G.P.	SM	Cult. or G.P.	SM	Cult. or G.P.	SM	Cult. or G.P.	SM	Cult. or G.P.	SM	Cult. or G.P.
a. Sputum												
b. Urine												
c. Pleural fluid												
d. Pericard. fluid												
e. Ascitic fluid												
f. _____												
Sp. gravity												
Protein												
Sugar												
Cell count												
g. _____												
Sp. gravity												
Protein												
Sugar												
Cell count												
h. *Blood*												
White count												
Red count												
Differential												
Chemistry:												

VOL 4 195

CASE REPORT FOR TUBERCULOUS PERICARDITIS (page 3) | CASE NO.

16. Clinical course	At start of Rx*	Months Post-Rx* 1	2	3	4	5	6	For Coding Purposes
a. Temp.								15.
b. Pulse								16.
c. B.P.								17.
d. Venous press.								18.
e. Cardiac pain								19.
f. Weight								20.

*If no Rx. report findings at admission and months post-adm. 21.

17. New Evidence of Tbc. (Specify date of onset) 22.

a. ☐ Pulm. Tbc _____ 23.

b. ☐ Pleurisy c Eff. ☐ Proven Tbc: ☐ Yes ☐ No _____ 24.

c. ☐ Tbc of pleura _____ 25.

d. ☐ Tbc of peritoneum _____ 26.

e. ☐ Miliary Tbc (Specify sites): _____ 27.

f. ☐ Other (Specify): _____ 28.

18. Manner of Disposition

☐ MHB ☐ AWOL ☐ AMA ☐ Disciplinary

☐ Transf to _____

☐ Died—Causes of death:

19. Follow-up Data on Last Observation

a. Date: _____

b. Work status: ☐ Full ☐ Half-time ☐ Less than half ☐ None

c. Cardiac disability ☐ Mild ☐ Mod. ☐ Severe ☐ None

20. Remarks:

OL.
4
956

REFERENCES

1. Falk, A., and Ebert, R. V.: Tuberculous Pericarditis Treated With Streptomycin, J.A.M.A. **145**:310, 1951.
2. Anderson, H. J.: Tuberculous Pericarditis, Brit. J. Tuberculosis **48**:12, 1954.
3. Wolfe, L. I.: An Autopsy Study of Diseases of the Pericardium, Permanente Found. M. Bull. **8**:122, 1950.
4. Griffith, G. C., and Wallace, L.: The Etiology of Pericarditis, Dis. Chest **23**:282, 1953.
5. Reeves, R. L.: The Cause of Acute Pericarditis, Am. J. M. Sc. **225**:34, 1953.
6. Hermann, G. R., Marchand, E. J., Greer, G., and Hejtmancik, T. R.: Pericarditis, Am. Heart J. **43**:641, 1952.
7. Peeble, R. B.: Etiology of Pericarditis, J.A.M.A. **37**:1510, 1901.
8. Diefenbach, W. C. L.: Tuberculosis of the Heart, Am. Rev. Tuberc. **62**:390, 1950.
9. Harvey, A. M., and Whitehill, M. R.: Tuberculous Pericarditis, Medicine **16**:45, 1937.
10. Goyette, E. M., Overholt, E. L., and Rappaport, E.: Treatment of Tuberculous Pericarditis, Circulation **9**:17, 1954.
11. Todd, R. McL.: Tuberculous Pericarditis, Arch. Dis. Childhood **26**:78, 1951.
12. Auerbach, O.: Pleural Peritoneal and Pericardial Tuberculosis, Am. Rev. Tuberc. **61**:845, 1950.
13. Stepman, T. R., and Owyang, E.: Clinically Primary Tuberculous Pericarditis, Ann. Int. Med. **27**:915, 1947.
14. Bouvrain, Y., and Pages-Darteville, S.: The Prognosis of Tuberculous Pericarditis, Semaine hôp. Paris **31**:831, 1955.
15. Sweaney, H. C.: Tuberculous Pericarditis Associated With Primary Pulmonary Tuberculosis, Dis. Chest **19**:521, 1951.
16. Thompson, W. P.: Primary Tuberculosis of the Pericardium, J.A.M.A. **100**:642, 1933.
17. Moore, J. A., and Murphy, J. D.: Constrictive Pericarditis With Tuberculous Intrapericardial Abscess Treated With Streptomycin, Ann. Surg. **127**:685, 1948.
18. Wood, J. A.: Tuberculous Pericarditis, Am. Heart J. **42**:737, 1951.
19. Shapiro, J. B., and Weiss, W.: Tuberculous Pericarditis With Effusion: The Impact of Antimicrobial Therapy, Am. J. Med. Sc. **225**:229, 1953.
20. William, C., and Soutter, L.: Pericardial Tamponade, Ann. Int. Med. **94**:571, 1954.
21. White, P. D.: Heart Disease, ed. 4, New York, 1951, The Macmillan Company, p. 713.
22. Janovsky, R. C., Boettner, J. F., Van Ordstrand, H. S., and Effler, D. B.: Recurrent Tuberculous Pericarditis, Ann. Int. Med. **37**:1268, 1952.
23. Proudfit, W. L., and Effler, D. B.: Diagnosis and Treatment of Cardiac Pericarditis by Pericardial Biopsy, J.A.M.A. **161**:188, 1956.
24. Sutliff, W. D., Hughes, F., and Rice, M. L.: Pleural Biopsy, Dis. Chest **26**:551, 1954.
25. Douglass, B. E., Carr, D. T., and Bernatz, P. E.: Diagnostic Thoracotomy in the Study of "Idiopathic" Pleural Effusion. Presented at the Annual Meeting of the National Tuberculosis Assn., New York, May, 1956.
26. Stead, W. M., Eichenholz, A., and Stauss, H. K.: Operative and Pathologic Findings in 24 Patients With the Syndrome of Idiopathic Pleurisy With Effusion, Presumed Tuberculous, Am. Rev. Tuberc. **71**:473, 1955.
27. Porter, W. B., Clark, O., and Porter, R. R.: Non-specific Benign Pericarditis, J.A.M.A. **144**:749, 1950.
28. Kotte, J. H., and McGuire, J.: Pericardial Paracentesis, Mod. Concepts Cardiovasc. Dis. **120**: No. 7, 1951.
29. Estes, E. H., Bishop, L. H., and McIntosh, H. D.: The Electrocardiogram as a Safeguard in Pericardial Paracentesis. Unpublished data.
30. Harrington, S. W.: Chronic Constrictive Pericarditis, Mod. Concepts Cardiovasc. Dis. **16**: No. 5, 1947.
31. Ritvo, M.: Chest X-Ray Diagnosis, Philadelphia, 1951, Lea & Febiger, p. 351.
32. McGuire, J., Kotte, J. H., and Helm, R. A.: Acute Pericarditis, Circulation **9**:425, 1954.
33. Meredith, H. C.: Streptomycin in Acute Tuberculous Pericarditis, Am. Heart J. **37**:129, 1949.
34. Tapie, J., Laporte, J., Pinel and Monnier: L'action de la Streptomycine dans le traitement des pericardites tuberculeuses, Presse méd. **58**:226, 1950.
35. Myers, T. M., and Hamburger, M.: Tuberculous Pericarditis: Its Therapy With Streptomycin and Some Observations on the Natural History of the Disease, Am. J. Med. **12**:302, 1952.

VOL 4 195

REPORT OF SYPHILIS FOLLOW-UP PROGRAM AMONG VETERANS AFTER WORLD WAR II

S. Ross Taggart, M.D.,* Stanley B. Russell, B.A.,** and Eleanor V. Price***

(Received for publication July 10, 1956.)

OL.
4
956

HOSPITALIZATION for approximately 5,000 veterans of World War I who developed insanity due to syphilis is now being provided by the Veterans Administration. Generally, these paretic patients have required hospitalization for many years. At present, in addition to these 5,000 patients with syphilitic psychoses, over 1,000 veterans with other crippling lesions of syphilis are occupying beds in Veterans Administration hospitals.

The average cost of maintaining a paretic patient in VA facilities is approximately $40,000. Other syphilitic cripples, chiefly from cardiovascular disease, require long-term hospitalization and add materially to the hospital monies expended.

The incidence of syphilis in the Armed Forces was high during World War II. Between 1940 and 1946 approximately 500,000 members of the Armed Forces had acquired or had been treated for syphilis. The Department of Medicine and Surgery, Veterans Administration, undertook a study, herewith reported, of the current status of veterans who had been treated for syphilis during World War II. It was felt that the results might benefit the individual, the community in which he lived, and the nation as a whole.

METHOD OF STUDY

At its inception, it was hoped that the Department of Medicine and Surgery of the Veterans Administration might itself conduct the syphilis follow-up program in all 500,000 Armed Forces infected veterans (400,000 Army and 100,000 Navy). However, legislative restrictions prevented the Veterans Administration from performing the actual investigative field work. Therefore state and local health departments were approached and, with assistance from the Venereal Disease Division of the United States Public Health Service, they agreed to investigate the cases referred for follow-up.

*Acting Chief, Preventable and Chronic Diseases Division, D. C. Department of Public Health: Consultant in Syphilology, Department of Medicine and Surgery, Veterans Administration.

**Social Economist and Survey Statistician in Charge of Veterans Administration Syphilis Follow-Up Program.

***Statistician, Venereal Disease Program, Division of Special Health Services, Public Health Service, U. S. Department of Health, Education, and Welfare, Washington, D. C.

Field investigation and study of all the 500,000 veterans could not be undertaken because of limited facilities and personnel. Thought was therefore given by the planning group to the problem of which types of cases would benefit most from follow-up. It was recommended that only the following groups be studied: (a) patients whose spinal fluid had not been examined; (b) those with previously recorded positive or doubtful spinal fluid findings; and (c) those who had received "inadequate" treatment. Eliminated were those whose treatment was considered "adequate" and those incompletely treated but who had already received adequate follow-up in the Armed Forces. By this selection, the patients to be studied were reduced to approximately 122,000.

In December, 1949, a letter explaining the purpose of the follow-up program was sent by the Chief Medical Director of the Veterans Administration to the cooperating State Health Departments. Simultaneously, a letter from the chief, Venereal Disease Division of the U. S. Public Health Service, Federal Security Agency (now Department of Health, Education, and Welfare) was addressed to all state health officers endorsing the program. The Veterans Administration then prepared abstracts of veterans' syphilis records for the groups of patients selected. The data on the abstract included the veteran's name and address, other identifying personal characteristics, date of and pertinent information relating to diagnosis, blood serologic and spinal fluid findings, and treatment during military service. The abstracts were prepared in quadruplicate to provide one copy to be returned to the Veterans Administration, one to be retained by the State Health Department, one to be retained at a local level, and one to be used by the venereal disease worker in his investigation.

It was thought that many veterans might have been examined by the health departments in the course of the regular venereal disease control program following their discharge from the Army. These veterans would not necessarily require reinvestigation as it was anticipated that in such cases the abstract forms could be completed from the follow-up data already on file. It was suggested that the remainder of the referred cases might be incorporated into the states' venereal disease control program.

The Syphilis Follow-up Program was in operation for approximately three years. The initial mailing of abstracts was made to the states in January, 1950. Additional abstracts were forwarded at intervals as they were completed. In December, 1952, the state health departments were advised that Jan. 31, 1953, had been designated as a closing date for tabulation of results, and they were requested to return as many outstanding abstracts as possible by that time. This report contains an analysis of all abstracts received up to that date. All states except one entered into some participation of the follow-up activities. Three states, after having submitted a small number of reports, advised the Veterans Administration that they were unable to continue their cooperation.

A total of 122,461 abstracts of syphilis registers were sent to state health departments. As of Jan. 31, 1953, a total of 90,293 (73.7 per cent) of these forms had been returned to the Veterans Administration. Table I shows the number of abstracts sent to and returned by each state.

VOL 4 195

TABLE I. NUMBER OF ABSTRACTS SENT OUT AND RETURNED AS OF JAN. 31, 1953

STATES	NUMBER SENT OUT	NUMBER RETURNED	PER CENT RETURNED
Alabama	5,354	4,330	80.8
Arizona	767	195	25.4
Arkansas	2,309	2,140	92.6
California	6,825	6,721	98.5
Colorado	857	737	86.0
Connecticut	1,455	686	47.2
Delaware	400	372	93.0
Dist. of Columbia	1,775	554	31.2
Florida	4,668	4,142	88.7
Georgia	6,791	1,212	17.8
Illinois	7,113	6,827	95.9
Indiana	2,695	2,598	96.4
Iowa	763	623	81.6
Kansas	1,295	612	47.3
Kentucky	3,665	1,291	35.2
Louisiana	5,149	4,745	92.1
Main	344	321	93.3
Maryland	1,378	835	60.6
Massachusetts	2,015	1,778	88.2
Michigan	3,986	3,955	99.2
Minnesota	958	824	86.0
Mississippi	5,463	4,737	86.7
Missouri	4,107	3,544	86.3
Montana	232	31	13.3
Nebraska	619	528	85.2
Nevada	129	128	99.2
New Hampshire	249	227	91.2
New Jersey	3,255	1,510	46.4
New Mexico	693	439	63.3
New York	6,553	5,897	90.0
North Carolina	6,427	3,955	61.5
North Dakota	191	86	45.0
Ohio	7,275	4,904	67.4
Oklahoma	2,006	1,679	83.7
Oregon	505	492	97.4
Pennsylvania	6,628	6,472	97.6
Rhode Island	276	243	88.0
South Carolina	3,459	755	21.8
South Dakota	165	87	52.7
Tennessee	4,637	2,706	58.4
Texas	1,146	32	2.8
Utah	191	143	74.8
Vermont	165	47	28.5
Virginia	3,747	2,543	67.8
Washington	742	734	98.9
West Virginia	2,039	2,003	98.2
Wisconsin	914	790	86.5
Wyoming	86	83	96.5
TOTAL	122,461	90,293	73.7

OL.
4
956

RESULTS

Information on 8,578 of the 90,293 abstracts returned by the states was limited to data on record prior to the syphilis roundup. On the remaining 81,715 patients, investigation was instituted by the states at the request of the Veterans Administration.

Table II indicates that 45 per cent of the veterans could not be located. This is not surprising since the home addresses were specified at the time of separation, which in most instances was five or more years prior to this survey. Twelve per cent were located but were apparently unwilling to submit to examination; 3 per cent were still in military service; 0.7 per cent were dead, and 5 per cent were closed for miscellaneous reasons.

TABLE II. RESULTS OF INVESTIGATIONS BY HEALTH DEPARTMENTS JANUARY, 1950 TO JANUARY, 1953, INCLUSIVE

RESULT OF INVESTIGATION	NUMBER	PER CENT	
Total investigated	81,715	100.0	
Unable to locate	36,791	45.2	
Located but not examined	9,788	11.9	
In service	2,685	3.3	
Deceased	640	0.7	
Closed for miscellaneous reasons	4,025	4.9	
Examined	27,786	34.0	
Serologic test for syphilis	27,786	100.0	
Positive	5,235		18.8
Doubtful	763		2.7
Negative	21,788		78.5
Spinal fluid examination	13,837	49.8	
Positive or doubtful	586		4.2
Negative	13,251		95.8

The remaining 34 per cent (27,786 veterans) were located and examined. All of these had a blood serologic test for syphilis (STS) and almost half of them a spinal fluid examination. In 18.8 per cent the STS was positive and in 2.7 per cent doubtful. The spinal fluid examination was positive or doubtful in 4.2 per cent of those examined.

As stated previously, follow-up was requested on three types of veterans who were treated for syphilis in the service; namely, those "inadequately" treated, those with a previously abnormal spinal fluid examination, and those who had failed to have a spinal fluid examination while in service. In the belief that the last of these three groups represents a cross section of veterans treated for syphilis, the analysis which follows is limited to this sample.

The group under consideration is further limited to veterans whose original service diagnosis was primary or secondary syphilis; to those who were untreated prior to induction; and to those who had a spinal fluid examination after separation from the Armed Forces. In spite of these limitations this group included 8,317 veterans.

Table III shows the number examined by each state and the number and per cent who had positive or doubtful spinal fluid examinations. "Positivity" is defined as a positive complement fixation or flocculation test, or a doubtful test associated with 20 or more cells. "Doubtful" includes a doubtful complement fixation or flocculation test with fewer than 20 cells, or no data as to cell count. Increased cell counts unaccompanied by abnormal complement fixation or flocculation tests have been disregarded.

TABLE III. PERCENTAGE OF ABNORMAL SPINAL FLUIDS AMONG VETERANS TREATED IN SERVICE FOR PREVIOUSLY UNTREATED PRIMARY OR SECONDARY SYPHILIS BY STATE PERFORMING EXAMINATION

STATE	TOTAL WITH SPINAL FLUID EXAMINATION	ABNORMAL CSF					
		DOUBTFUL*		POSITIVE†		TOTAL	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Alabama	157	—	0.00	1	0.64	1	0.64
Arizona	5	—	—	—	—	—	—‡
Arkansas	246	3	1.22	2	0.81	5	2.03
California	626	3	0.48	11	1.76	14	2.24
Colorado	42	—	0.00	—	0.00	—	0.00
Connecticut	155	—	0.00	2	1.29	2	1.29
Delaware	26	—	0.00	—	0.00	—	0.00
Dist. of Columbia	68	2	2.94	—	0.00	2	2.94
Florida	181	1	0.55	3	1.66	4	2.21
Georgia	187	1	0.53	9	4.81	10	5.35
Illinois	759	2	0.26	11	1.45	13	1.71
Indiana	213	3	1.41	9	4.23	12	5.63
Iowa	18	—	—	—	—	—	—‡
Kansas	46	—	0.00	—	0.00	—	0.00
Kentucky	161	2	1.24	3	1.86	5	3.11
Louisiana	234	1	0.43	9	3.85	10	4.27
Maine	47		0.00	1	2.13	1	2.13
Maryland	92	—	0.00	8	8.70	8	8.70
Massachusetts	507	—	0.00	1	0.20	1	0.20
Michigan	379	1	0.26	3	0.79	4	1.06
Minnesota	33	—	0.00	1	3.03	1	3.03
Mississippi	692	1	0.14	9	1.30	10	1.45
Missouri	276	1	0.36	6	2.17	7	2.54
Montana	1	—	—	—	—	—	—‡
Nebraska	93	—	0.00	2	2.15	2	2.15
Nevada	3	—	—	—	—	—	—‡
New Hampshire	23	—	0.00	—	0.00	—	0.00
New Jersey	185	—	0.00	2	1.08	2	1.08
New Mexico	32	—	0.00	—	0.00	—	0.00
New York	528	8	1.52	10	1.89	18	3.41
North Carolina	483	1	0.21	4	0.83	5	1.04
North Dakota	3	—	—	—	—	—	—‡
Ohio	364	—	0.00	2	0.55	2	0.55
Oklahoma	142	1	0.70	1	0.70	2	1.41
Oregon	38	—	0.00	—	0.00	—	0.00
Pennsylvania	331	6	1.81	11	3.32	17	5.14
Rhode Island	17	—	—	—	—	—	—‡
South Carolina	83	—	0.00	1	1.20	1	1.20
South Dakota	5	—	—	—	—	—	—‡
Tennessee	132	—	0.00	—	0.00	—	0.00
Texas	6	—	—	1	—	1	—‡
Utah	27	—	0.00	—	0.00	—	0.00
Vermont	4	—	—	1	—	1	—‡
Virginia	261	2	0.77	7	2.68	9	3.45
Washington	112	1	0.89	4	3.57	5	4.46
West Virgina	226	1	0.44	3	1.33	4	1.77
Wisconsin	66	1	1.52	2	3.03	3	4.55
Wyoming	2	—	—	—	—	—	—‡
TOTAL	8,317	42	0.50	140	1.68	182	2.19

*Doubtful—C.F. Doubtful, less than 20 cells or cell count not done.
†Positive—C.F. positive or C.F. doubtful with 20 or more cells.
‡Less than 20 veterans examined.

OL.
4
956

Of the 8,317 veterans included in the analysis, 140 (1.7 per cent) had positive spinal fluid examinations and 42 (0.5 per cent) were doubtful (as defined), a total of 2.2 per cent.

Twenty-six per cent of the veterans in the group under analysis had been treated in the Armed Forces with a minimum of 4,800,000 units of penicillin or 40 arsenical injections; 99.8 per cent received a minimum of 2,400,000 units of penicillin or 20 arsenical injections. Since 7,132 (86 per cent) of the 8,317 veterans were still in the primary stage of syphilis when treatment was initiated, the spinal fluid positivity rate of 2.2 per cent may be considered the rate of occurrence of positive (or doubtful) spinal fluids following the administration of what is generally believed to be sufficient treatment for early syphilis.

A group of 658 veterans either received more than one course of treatment in service or were retreated at some later time between separation and the follow-up examination. As a whole, it cannot be determined whether this group is composed of patients whose initial course of treatment was unsuccessful or who were reinfected. The abnormal spinal fluid rate in this group was 6.84 per cent (6.23 per cent positive and 0.61 per cent doubtful). The rate among veterans who, as far as is known, received only the original treatment was 1.79 per cent (1.29 per cent positive and 0.50 per cent doubtful).

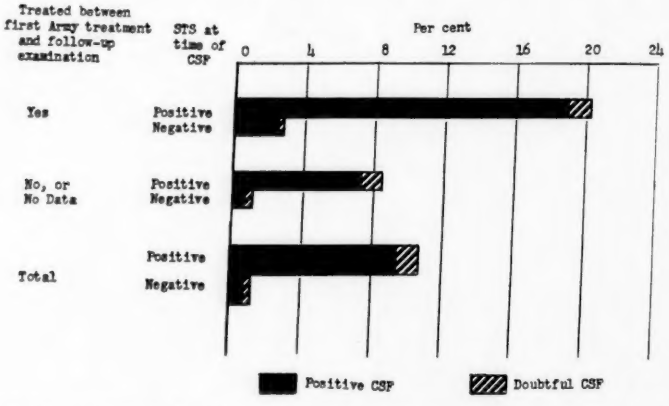


Fig. 1.—Spinal fluid positivity as related to serologic status and treatment between first Army treatment and follow-up examination.

Veterans whose blood test for syphilis was positive at the time of the spinal fluid examination had the highest percentage of abnormal spinal fluids. As shown in Fig. 1, slightly over 20 per cent of veterans who were treated between the original Armed Forces treatment and the follow-up examination and whose STS was still positive had abnormal spinal fluids tests (18.95 per cent positive and 1.31 per cent doubtful). In the group whose STS was negative, the abnormal spinal fluid rate dropped to 2.80 per cent (2.51 per cent positive and 0.29 per cent doubtful).

Among veterans who received only the original Armed Forces treatment, the percentage with abnormal spinal fluids was 8.46 when the STS was positive and 1.10 when the STS was negative. The ratio of doubtful to positive was 1

to 6 when the STS was positive and 5 to 8 when the STS was negative. This large proportion of doubtful tests in veterans with negative STS is suggestive of laboratory error. It is also possible that some of the positive spinal fluids associated with negative STS represent veterans treated in the intervening years whose blood reversed to negative prior to reversal of the spinal fluid. Since the follow-up form submitted to the states did not specifically request all data available, some states furnished the result of the requested follow-up examination only. Whatever the explanation, 49 (39 per cent) of the 140 positive spinal fluids discovered during this survey were found in veterans whose blood tests were negative (Table IV).

TABLE IV. PERCENTAGE OF ABNORMAL SPINAL FLUIDS IN WHITE AND NEGRO MEN BY RESULT OF STS AT TIME OF SPINAL FLUID EXAMINATION

RACE AND SEX	RESULT OF STS	TOTAL WITH CSF EXAMINATION	ABNORMAL SPINAL FLUID					
			DOUBTFUL		POSITIVE		TOTAL	
			NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
White Male	Positive	260	2	0.77	27	10.38	29	11.15
	Negative	3,597	18	0.50	30	0.83	48	1.33
	Not done	817	5	0.61	6	0.73	11	1.35
	TOTAL	4,674	25	0.53	63	1.35	88	1.88
Negro Male	Positive	554	8	1.44	50	9.03	58	10.47
	Negative	2,644	8	0.30	19	0.72	27	1.02
	Not done	395	1	0.25	8	2.03	9	2.28
	TOTAL	3,593	17	0.47	77	2.14	94	2.62
TOTAL (including other or unknown)	Positive	815	10	1.23	77	9.45	87	10.67
	Negative	6,284	26	0.41	49	0.78	75	1.19
	Not done	1,218	6	0.49	14	1.15	20	1.64
	TOTAL	8,317	42	0.50	140	1.68	182	2.19

The spinal fluid positivity rate was higher in Negro men than in white men. However, (Fig. 2 and Table IV) the difference is reversed when the STS is considered. Of the 4,674 white men, only 260 had a positive STS, whereas the STS was positive in 554 of the 3,593 Negro men. This difference probably indicates a higher reinfection rate among Negro men.

In general, the longer the time elapsing between the initial treatment and the follow-up examination, the higher the percentage with positive spinal fluid tests. As seen by the solid bars in Fig. 3, which is limited to veterans actually examined during the roundup from 1950 to 1953, the spinal fluid positivity rate increased from 1.02 per cent of those examined two to four years following treatment to 3.24 per cent of those examined eight to ten years following treatment.

Veterans with the shortest observation period were treated with penicillin; those with the longest observation period received arsenoxide and bismuth.

The two methods of treatment overlap in veterans examined six to eight years following treatment. At this time, 2.88 per cent treated with penicillin had positive spinal fluid tests as compared with 2.07 per cent treated with arsenoxide and bismuth. Although the difference of 0.81 per cent is not statistically significant at the 5 per cent level, there is certainly no indication that penicillin, as utilized by the Armed Forces, was any more effective than arsenoxide and bismuth in preventing neurologic involvement.

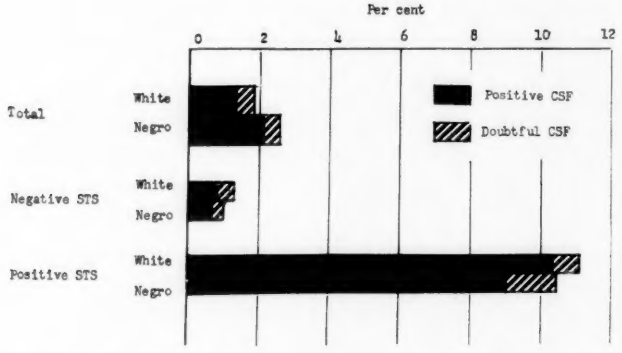


Fig. 2.—Comparison of spinal fluid positivity rate between white and Negro male veterans.

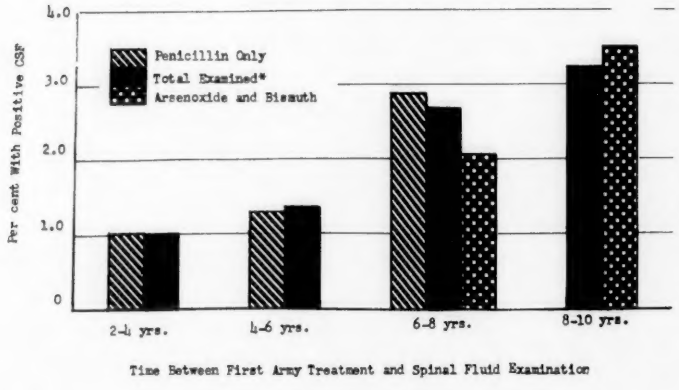


Fig. 3.—Per cent of veterans with positive spinal fluid examination by type of Army Treatment and time between first Army treatment and spinal fluid examination.

In the penicillin-treated group, the increase in spinal fluid positivity from 1.29 per cent at 4-6 years to 2.88 per cent at 6-8 years is statistically significant. It might be reasoned that the increase merely reflects a change in the penicillin schedule employed. It is true that as experience was gained and penicillin became more plentiful, the standard Armed Forces schedule was increased from 2,400,000 units to 6,000,000 units or more. Only 1.7 per cent of those examined

6-8 years following treatment had received the larger dosage schedules as compared with 16 per cent of those examined 4-6 years following treatment and 84 per cent of those examined 2-4 years following treatment. However, when the data are limited to patients treated with 2,400,000 units, a significant increase still occurs between those examined 4-6 years and those examined 6-8 years following treatment.

Those familiar with the history of penicillin in the treatment of syphilis will recall the decreasing efficacy of penicillin in this period. With changes in the mold utilized and methods of growing it in 1944 and 1945, the penicillins produced contained large amounts of the K form. It was later determined that penicillin K was less effective than penicillins G, F, and X. Most penicillin manfactured after 1946 was crystalline G, which is the penicillin of choice for the treatment of syphilis. It is believed that the K factor too, is reflected in the spinal fluid positivity rates. For example, 3.0 per cent of patients treated in 1946 with 8,000,000 units or more had positive spinal fluids when re-examined from 1950 to 1953. Among patients treated with the same dosage in 1947, after crystalline penicillin G had become available, only 0.4 per cent were found to have positive spinal fluid on re-examination. Unfortunately, the majority of the veterans treated with penicillin were treated in 1945 and 1946, during the period of uncertainty.

DISCUSSION

The foregoing data suggest that 3 per cent is a minimum estimate of the amount of neurosyphilis to be found among veterans treated for syphilis during World War II. First, this estimate is based on veterans treated for new infections (previously untreated primary and secondary syphilis) which are most amenable to treatment. Second, more than 99 per cent of the cases analyzed received at least the minimum recommended for early syphilis. Third, the estimate is based on an observation period of 8-10 years. Since the per cent with positive spinal fluids appears to increase with the duration of observation, and as the period following World War II is extended 10 or 20 years, it is possible that a further increase in the spinal fluid positivity rate may be expected.

If this rate of 3 per cent is applied to the 500,000 veterans treated for syphilis while in service, a minimum of 15,000 are estimated to have spinal fluid evidence of neurosyphilis at the present time.

Of these 15,000, some will die before the disease progresses to a point requiring hospitalization; others will subsequently receive sufficient treatment to halt progression without hospitalization.

The syphilis case-finding program, applicable both to veterans and to the general population, which is directed toward finding persons at the risk of the disabling and potentially fatal risk of neurosyphilis, has, in recent years, moved more slowly, as financial resources became more limited and lowered incidence and prevalence made case finding more difficult and costly. We may therefore anticipate as the average age of the syphilis reservoir increases, a continued substantial group of persons, veterans and civilians, who will require the expensive care implied in neurosyphilitic progression.

Acknowledgment for help and advice is made to the following members of the Department of Medicine and Surgery of the Veterans Administration: Dr. Bascom Johnson, Jr., Chief, Dermatology and Syphilology Section; Dr. E. H. Cushing, Director, Research and Education Service; Mr. Morton Robins, Chief, Biometrics Section, Medical Statistics Division; and Drs. E. R. Gentry and M. Z. Cooper, Chief and Section Chief, Medical Division; and also to Miss Lida J. Usilton, Formerly Public Health Administrator, Division of Special Health Services; now, Field Health Services Branch, Division of Indian Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

Gratitude is expressed to the various State Health Departments for the effort that they put forth in locating and examining the almost 28,000 men who are reported on in this study.

VOL.
4
1956

STATISTICAL APPROACHES TO THE STUDY OF CANCER WITH PARTICULAR REFERENCE TO CASE REGISTERS

WILLIAM HAENSZEL, M.A., AND NOKA B. HON, M.D.

BETHESDA, MD.

From the Biometry and Epidemiology Branch and Field Investigations and Demonstration Branch, National Cancer Institute, Public Health Service, U. S. Department of Health, Education and Welfare

(Received for publication July 17, 1956.)

THE purpose of this paper is to offer some observations on the role of case registers, particularly their use as a research tool, in studies of cancer. Case registers are but one of several study techniques, and a balanced discussion requires a brief review of other methods employed in the study of cancer in human populations. The experimental method has limited application to human populations; work of this type relating to cancer will be encountered in the field of therapeutic trials, but usually not in the study of carcinogenesis. The remaining approaches appear, from a methodologic point of view, to fall into six major categories: (1) analyses of mortality data, (2) retrospective studies of diagnosed cases and matched controls, (3) forward studies of defined cohorts, (4) morbidity surveys, (5) screening of populations for precursive signs, and (6) case register operations.

The classification is a general one, not unique for cancer, and need not even be limited to the topic of health and illness. The scheme could readily be adapted to studies covering a wide spectrum of conditions and activities in the life of man. Some illustrations of the use of each technique in the study of cancer, drawn for the most part from work by persons connected with official and voluntary health agencies, are sketched below. The references cited are not intended to be complete or exhaustive. The citation of several papers dealing with lung cancer reflects greater activity in epidemiologic investigations concerned with neoplasms in that site.

Analysis of Mortality Data.—Reports prepared by vital statistics offices contain a great deal of basic information on the distribution of cancer mortality by age, sex, race, and other demographic variables. While questions have been raised concerning the adequacy of medical certifications of death, inferences from mortality data have often proved consistent in many respects with those based on information from other sources. Their chief weakness has been that mortality data for specific primary sites have not been tabulated routinely in sufficient age and sex detail for states and small geographic subdivisions. Also, mortality data alone cannot answer questions concerning survival experience and how it varies among specific categories of diagnosed cases.

The increasing importance of cancer as a cause of death was noted by Schereschewsky[1] in 1925 after he examined death registration data for a twenty-one-year period. A more comprehensive, systematic report on cancer mortality in the United States was later prepared by Gover[2] and still is a useful reference. A later publication of the National Office of Vital Statistics, covering the years 1940 to 1945,[3] may be regarded as a supplement to the Gover report. Recently, more attention has been devoted to the examination of urban-rural differentials. Spiegelman's[4] analysis of United States data revealed a varying pattern of urban-rural gradients for specific cancer sites. It seems unlikely that the urban-rural differentials observed are all artifacts produced by differences in diagnostic and medical care facilities. Hoffman and Gilliam,[5] in their investigation of lung cancer mortality, adjusted their rates for individual states to take account of urban-rural residence and race as well as sex and age, a practice likely to be followed by others in the future.

The forthcoming presentation of the 1950 United States mortality data according to the usual occupation and industry of the decedent should supply further leads on cancer risks associated with occupation. The results will be in a form patterned after that used by the Registrar-General in presenting data for England and Wales,[6-8] which have long been a standard source of information on this topic.

Exploitation of cancer mortality data for epidemiologic studies which depart from the beaten track of standard analyses dates back at least to Lombard and Doering.[9] In 1927, they noted different urban-rural patterns of cancer mortality for several sites, adjusted for age, in the native- and foreign-born population of Massachusetts.[9] They later interpreted these findings as being associated with differences in economic status.[10] In the same vein, Mancuso and co-workers[11] recently found in Ohio a difference in lung cancer mortality between the native-born and foreign-born population. Comparisons of migrant and native-born populations have been made elsewhere. Results for New Zealand published by Eastcott[12] show marked differences in lung cancer mortality between the indigenous population and migrants from Great Britain, which are not duplicated for other cancer sites.

An interesting application of mortality data is provided by Buechley and co-workers.[13] Taking advantage of a special Census Bureau classification of population of Mexican descent by means of Spanish surnames, the authors classified lung cancer deaths in California in the same manner. They were thus able to confirm Steiner's observation from autopsy data of an unusual sex ratio for lung cancer deaths among Mexicans[14] and to show further that this was due to high lung cancer death rates among women born in Mexico.

The range of population characteristics for which specific mortality rates can be computed may be extended in the future through coordinated collection of additional information for dual samples of populations and deaths. The Current Population Survey of the United States Bureau of the Census offers a means for collecting additional population data on a national or regional basis for use with data which may be obtained by querying the attending physician and relatives of the decedent.[15]

Retrospective Studies.—Retrospective studies call for the collection of histories about suspect antecedent events from a series of diagnosed cases and from controls matched or stratified with respect to age, sex, and other pertinent characteristics. This relatively inexpensive method is favored by clinical investigators, since it is adapted to their study material and resources. When a disease occurs rarely or infrequently, this may be the only possible approach, since the expense of assembling and tracing a large population exposed to a suspected agent to yield sufficient cases for a direct measure of risk may prove prohibitive.

The findings from a retrospective study "proceed from effect to cause and not from cause to effect."[16] However, if the diagnosed cases are representative of all persons developing the disease under the conditions specified and the controls are likewise representative of all persons not developing the disease, the effect of an antecedent factor in altering the probability of developing the disease may be estimated. Here, the choice of an appropriate control population is crucial. The assumptions and the procedures for estimating relative risks, and under certain conditions absolute risks, have been discussed by Cornfield.[17]

OL.
4
956

Lombard and Doering[18] were among the first public health workers to make retrospective studies on cancer. In view of later reports of an association between smoking and lung cancer, it is interesting to note that in 1928 they observed that smokers showed an excess risk for cancer of all sites. The number of diagnosed lung cancer cases available at that time was too small for study. Lung cancer and smoking are the site and agent for which the retrospective method has been used most extensively[19] and workers in health agencies have contributed their share of the total output.[20,21]

The retrospective technique is being applied to studies of occupational factors.[22,23] This removes the limitation, inherent in mortality data, of classification by usual occupation only and permits examination of the total history of occupational and industrial exposures.

The retrospective approach will be employed more frequently in the future for studies of carcinoma-in-situ and invasive uterine cancer. The expanding use of vaginal cytology as a screening device and control measure would automatically provide large numbers of cases and controls from whom more detailed histories may be taken. The paper of Wynder and his associates[24] illustrates the retrospective approach in a study of the etiology of cervical cancer.

Forward Study of Selected Cohorts.—The basic steps in a forward study are to define a group of people (cohort) as of a fixed point in time, to classify them with regard to certain characteristics, and to follow them forward in time to determine their fate. The definition and assembly of a cohort need not be done contemporaneously. If comprehensive records about a group exist and their coverage has not been distorted by selection and retention with respect to subsequent events, a cohort may be traced forward from a past date fixed in the records. The results of follow-up can be expressed directly as rates by relating counts of subsequent events to the original population base. The choice of a cohort is conditioned by the nature of the suspected carcinogen. While the decision to undertake a study is usually motivated by issues concerning a

specific cancer site, a bonus is provided by information about other sites and other diseases, since follow-up automatically yields these other data. The American Cancer Society study finding (to date) of excess mortality among smokers for sites other than lung and for coronary disease[25] is an illustration. This is one reason why forward and retrospective studies complement each other so well, a point stressed by White and Bailar.[26]

Study cohorts may be assembled in a variety of ways. Hammond and Horn[25] used volunteers to collect smoking histories from people known personally to the volunteer workers. The same workers have at regular intervals supplied data on deaths occurring among persons they interviewed. The National Cancer Institute gained access to an insured population for whom deaths are reported as regular administrative routine.[27] The insured population was queried in advance of the observation period about smoking history, residence, and occupation. There are situations in which the information needed to classify persons may already be available and no special collection of data is entailed. This seems to be the case in some forward studies involving members of religious orders.

The approach can be applied to industrial carcinogens. Workers in the chromate industry have been studied in this fashion.[28] A cohort of 1,100,000 railroad workers has been followed since 1952. Specific studies in many other industries are possible. In undertaking them, the problem which presents the greatest difficulty is the rearrangement of records of administrative actions to relate them to individuals.

Forward studies may also cast light on suspected associations of cancer with other diseases. Mustacchi and Shimkin,[29] for example, have followed cases of acromegaly and hypopituitarism subsequent to the time of diagnosis and found that their cancer experience did not differ significantly from that of the general population.

Morbidity Surveys.—Cancer morbidity surveys conducted to date have relied on a canvass of certain sources of diagnostic information—physicians and hospitals. Only in this manner can the details on primary site, histologic type, microscopic confirmation, and other items be secured. For this reason it is unlikely that household surveys, which ask respondents to relate the facts concerning illness for members of households sampled, will ever be used extensively for epidemiologic studies of cancer. For the purposes of computing incidence and prevalence rates, the canvass of diagnostic sources for the population under study must be exhaustive to ensure coverage of practically all the diagnosed cases. Experience has shown that morbidity surveys yield more reliable results on incidence—cases diagnosed for the first time in the survey year—than on prevalence—the total number of persons with cancer. Incidence and prevalence rates may be computed for individual primary sites by sex, age, race, and other population characteristics. Newly diagnosed cases, if arrangements are made to follow them, may be used for investigations of survival experience.

The most comprehensive studies of this kind are the two surveys in 1937 and 1947 of ten metropolitan areas conducted by the National Cancer Insti-

tute.[30] More recently, tnis survey technique has been extended to an entire state, Iowa, and found to work for rural populations also.[31] The data collected yield information on intracity variation by census tract or other subdivisions[32] as well as for intercity and urban-rural differences. While it is usually economical to collect data for all cancer sites, the method can be employed for a specific site. A survey in Memphis was restricted to an enumeration of uterine cancer cases alone.[33]

Screening of Populations.—Morbidity surveys are concerned with diagnosed cases. The screening of populations for undiagnosed cases or precancerous conditions is an obvious extension of this approach. While the search for undiagnosed cancer cases or precursors could, in theory, be based on clinical history, observation, or examination, it will usually depend on the application of a specific test, either singly or as one of a battery of tests. Since no test procedure is completely accurate or reliable, all suspected cases or precursive conditions need to be confirmed. In common with screening procedures for other diseases, the general problem of false positives and false negatives must be considered in the interpretation of results.

The use of vaginal cytology to detect unsuspected carcinoma-in-situ or invasive uterine cancer[34,35] is perhaps the most interesting current example of population screening. The repeated collection of cytology specimens for women negative on first examination will permit a direct observation of the incidence of carcinoma-in-situ. This is being attempted in Memphis.[36] Even for populations screened once, it may be possible to take prevalence data as of a specific date and, by assuming that the results by age groups represent cumulative effects, to estimate a schedule of incidence rates required to produce the observed prevalence.

When a suspected precancerous condition has been defined, the follow-up of untreated patients can determine whether such persons do, in fact, have an excess risk of developing a specific cancer and the magnitude of the excess risk. However, once a condition is accepted as precancerous in nature, ethical considerations forbid withholding of treatment. For this reason it is now difficult to assemble a series of untreated carcinoma-in-situ cases for observation. The problem of the relationship of carcinoma-in-situ to invasive uterine cancer can be attacked in another manner. If carcinoma-in-situ is a precursor, then the large-scale detection and treatment of this lesion should result ultimately in a marked reduction of invasive uterine cancer in a study population. The Memphis field trial will yield information on this point. This principle has obvious applications to the study of other suspected precursors.

The significance of certain chest x-ray findings has been studied through the follow-up of untreated cases. Reports have appeared in the clinical literature on the subsequent fate of selected patients with pulmonary coin lesions. Lesions of possible neoplastic significance found in community chest x-ray surveys are now being followed to determine the future yield of lung cancer cases among persons showing such lesions.

Cancer Registers.—Cancer registers are maintained by many large hospitals, particularly research and teaching institutions. The American College of

Surgeons' requirements for approval of a cancer program[37] will encourage more hospitals to install them. The need to include in these registers data on outpatient cases is a point which should be stressed. Hospital registers have supplied data for several papers which have appeared in the clinical literature.

Central cancer registers are maintained by several state health departments. These state registers vary in scope of coverage and method of operation. They may attempt both reporting and follow-up of all diagnosed cases to secure incidence and survival data, as in Connecticut,[38] or complete reporting of cases without follow-up, as in upstate New York,[39] or reporting from selected institutions with follow-up so that survival but not incidence data are available, as in California and Saskatchewan.[40]

The tracing of cases reported to the register to determine survival status is, in itself, a forward study. An interesting example of a special type of forward study, which has been reported from Saskatchewan,[41] was concerned with the determination of the risk of developing a cancer in a second primary site among "cured" patients.

Cancer registers and morbidity surveys can produce the same kind of information. For cumulating data over long periods of time, reporting to a register should prove preferable to an active canvass for cases. The data supplied by the Connecticut register on trends in cancer incidence and survival are particularly valuable.[38] Since incoming reports are screened against names already on file, the risk of a register accepting a previously diagnosed case as one newly diagnosed is smaller than in morbidity surveys. However, a register depends on continued close cooperation by persons and organizations providing reports and may be more vulnerable to underreporting of cases than a morbidity survey. To guard against deterioration in the quality of data in central registers, close liaison must always be maintained with reporting sources.

As is the case with registration of births and deaths and compulsory reporting of communicable and other diseases, the detail available on personal characteristics, diagnosis, and treatment is severely limited. The difficulty may be overcome by collecting supplementary information for samples of cases drawn from the register. Used in this fashion, registers could prove a valuable source for detailed studies on effects of therapy and on the epidemiology of specific sites. Furthermore, the value of such special investigations would be enhanced by relating them to the incidence and survival data provided by the source material in the register. A program of special studies to supplement the basic register information is being developed in Connecticut.

DISCUSSION

The point which stands out in review is the interlocking nature of the study approaches. For example, leads on the association of cancer of a specific site with environmental exposures or personal characteristics may turn up in mortality, survey, or register data. These can then be pursued in further detail by means of retrospective or forward studies. Or, findings from retrospective or forward studies of special groups may be checked for consistency with more broadly based information on morbidity, mortality, and associated charac-

VOL
4
195

teristics from register, survey, and census data.[42] Registers, surveys, and death indices are necessary adjuncts to screening of populations, since they supply follow-up data on cohorts assembled and classified according to screening results. Registers and surveys also have forward study aspects, since they define cohorts of diagnosed cases for follow-up with respect to survival status. For any specific study the choice of a data collection method will depend on the nature of the question and the relative merits and disadvantages of alternate procedures. Studies of disease in human populations might be likened to a game of golf. Investigators have in their bags a variety of clubs representing study approaches. The problem is the choice of a correct combination of clubs and shots needed to complete the study course in par.

There is agreement on the role of each approach and the situations in which they should be attempted, with the exception, possibly, of case registers. The analysis of mortality data is a standard practice expected of all health departments and vital statistics offices, and everyone agrees that information procured through the death registration system should be exploited to the fullest extent.

For a retrospective study there must be a hypothesis to be tested. To begin one, history forms covering specific items must be developed, and this requires that the investigator have ideas on the expected findings and how they may test the hypothesis. Clearly, these fall into the category of special studies.

The assembly and tracing of selected cohorts is expensive and time-consuming. Although some cohorts may be followed as administrative by-products of business management or insurance plans, the rearrangement of records maintained for other purposes is not easy. Even when the exact nature of the response to the exposure under study is uncertain and the subject of a scientific fishing expedition, some effect is expected, so that the decision to follow a cohort prospectively is usually the outcome of a desire to do a special study.

Morbidity surveys cannot be construed as routine, repetitive operations, since they require protracted negotiations with medical societies, hospital associations, and health departments. They are expensive, and both financial and technical considerations place them in the category of special studies. Screening of populations presumes the existence of a test procedure. If a screening test has shown promise in pilot trials only, its application to large populations is a phase of operations research, and thus a special study, until it becomes a proved and accepted public health procedure.

Case registers remain. Is cancer case reporting a routine public health procedure, a counterpart of death registration, or communicable disease case reporting? Is it a service function or a research tool? The answer to this question must distinguish between case registers maintained by hospitals or local institutions and state health departments.

The maintenance of case registers in hospitals can be defended as a necessary service to the hospital, physician, and patient. The views of the American College of Surgeons on the need for cancer registers in hospitals are persuasive.[37] These service functions of a hospital register might also be met by a central register operated locally on behalf of several cooperating institutions. However, experience with the more remote central registers maintained in the offices

of state health departments has demonstrated no similar service role. Their work is not geared to the identity of individual patients; they deal with statistics, not individuals, and are essentially research tools. One thought which has been advanced is that state health departments need to operate central registers to ensure a pool of technical skills and services to provide consultant advice on registers to hospitals and local health departments. This argument loses some of its force when one recalls other fields in which states have successfully supplied consultation service without carrying on a corresponding program of operations at the state level, such as tuberculosis registers and the organization of public health nursing records.

Research needs do not require that central registers be maintained by all state health departments; 48 registers would not yield 48 times as much information. It is desirable, however, that several states in different regions of the country operate central registers so that results may be cross-checked and examined for consistency or evidence of divergent state and regional patterns. Before a state decides to establish a central register or to channel the equivalent money into other cancer service or study activities, the following points should be considered:

1. Central registers are expensive. The basic cost of operation, not counting fees or subsidies to hospitals to cover their reporting costs, will not be less than $2.50 to $4.00 per newly diagnosed case per year. This figure will vary depending on the salary scale and the method of cost accounting, particularly on how central overhead costs are allocated. Follow-up of surviving patients at annual intervals contributes to the total cost, but maintenance of central files for elimination of duplicates, follow-back for incomplete or missing data, resolution of contradictory information, revision of coded data to meet changing concepts, and tabulations for routine, periodic reports all entail sizable expenditures. The cost range cited does not allow for full exploitation of data in the form of occasional monographs or more intensive investigation of selected samples of cases.

2. Nothing is gained and everything is lost by skimping on cost, since the value of the register depends on complete reporting. Where reporting is inadequate, the interpretation of the assembled data becomes so equivocal as to be almost worthless. Rather than do an indifferent job for an entire state, it would be preferable to concentrate on collecting adequate and complete data for part of a state.

3. For the greatest return on money spent, there should be complete coverage of all reporting sources for an area for which population census data exist so that incidence as well as survival data can be obtained. The comment in the preceding point applies here. Major emphasis should be placed on securing reports for patients receiving any hospital service. Increased use of hospitals fostered by the growth of Blue Cross and other hospital insurance plans may in the future lessen the importance of receiving reports for cancer patients seen only in physicians' offices.

4. One alternative to a highly centralized state register might be stressed. Decentralized registers operated locally on behalf of cooperating hospitals and

physicians could fulfill a service function as well as meet some research needs. It is well known that the quality of reported data, when of immediate use and benefit to participants, is superior to those where the concern is long-range and remote, such as in the production of statistics. Where active service programs exist or can be fostered, decentralization of responsibility and administration may materially improve the quality of cancer register data.

A local, grass roots approach would not foreclose the possibility of establishing a central register. To the contrary, if events led later to the creation of a central register, the state health department would have gained a fund of experience and be in a better position to define its needs and objectives and to develop a suitable pattern of procedures. The point to remember is that a successful central register depends on its sources of information, not the converse. Given good local registers, the data for a state or a major subdivision might even be assembled by periodic field surveys, filling in gaps in the data when necessary, rather than by maintaining a permanent, central register organization. This course has been followed in some states to gather statewide information on tuberculosis cases and contacts.

OL.
4
956

5. Qualified personnel are in short supply. At present there are not enough epidemiologists and statisticians to meet the demands which would be entailed by a large expansion in the number of central cancer registers. While more persons could be recruited and trained, there are competitive demands for people to do studies of other chronic diseases which must also be satisfied.

6. In view of the expense of conducting the standard register operations, it would be wasteful not to include a program of special, collateral studies utilizing the register data. Experience in Connecticut indicates that such a program of special studies costs as much as the maintenance of register routines—about $4.00 per newly diagnosed case per year. Clearly, a coordinated program of basic data plus special studies in one state is more valuable than the collection of standard register data alone in two separate states. Interested states should explore the possibilities of securing supplementary technical and financial support before committing themselves to a case register operation.

The types of special studies which might be undertaken fall into three categories:

A. Exploitation of data reported to the register and other information routinely collected by the health department, such as: studies of causes of death and trends in mortality experience among "long-term" survivors; collection of data on multiple primaries; and reconciliation of information on cancer incidence, case fatality, and mortality provided by the register and the vital statistics death registration system.

B. Those requiring review of hospital records for supplemental data, namely: evaluation of therapy; natural history of disease in untreated patients and those treated palliatively; and collection of unusual cohorts for follow-up (for example, patients with plastic inserts).

C. Those requiring additional data from patients, relatives, and other sources, namely: retrospective studies on samples drawn from the register; and studies of familial distribution of cancer of specific sites.

The tenor of this discussion, then, is that a decision of a health department or other agency to start a state cancer register should not be an automatic one. The desirability of a balanced program using a variety of study approaches, illustrated by the golf game analogy, ought to be kept in mind. This calls for a review of resources within the state and a search for promising study situations preliminary to a determination of the types of investigations to be fostered. Some thought should be given to how epidemiologic investigations conducted under the sponsor's auspices may best be related to work done elsewhere. Initative on the part of investigators, who plan studies based on their interests and local opportunities, plus informal discussion among these same investigators on the interrelationship of findings will take advantage of the diversity of administrative and study approaches which our federal system permits and which fruitful scientific work requires.

VOL 4 195

REFERENCES

1. Schereschewsky, J. A.: The Course of Cancer Mortality in the Ten Original Registration States for the 21-year Period, 1900-1920, Pub. Health Bull. No. 155 (1925).
2. Gover, M.: Cancer Mortality in the United States. I. Trend of Recorded Cancer Mortality in the Death Registration States of 1900 From 1900 to 1935. II. Recorded Cancer Mortality in Geographic Sections of the Death Registration States of 1920, From 1920 to 1935. III. Geographic Variation in Recorded Cancer Mortality for Detailed Sites, for an Average of the Years 1930-32. IV. Age Variation in Mortality From Cancer of Specific Sites, 1930-32, Pub. Health Bull. No. 248 (1939), 252 (1940), 257 (1940), and 275 (1941).
3. U. S. Public Health Service: Cancer Mortality in the United States, Vital Statistics-Special Reports **32**:1, 1951.
4. Spiegelman, M.: Demographic Differentials in Cancer Mortality in Urban and Rural Areas of the United States, 1940, Vital Statistics-Special Reports **33**: No. 14, 1952.
5. Hoffman, E. F., and Gilliam, A. G.: Lung Cancer Mortality, Pub. Health Rep. **69**:1033, 1954.
6. Logan, W. P. D.: Social Class Variations in Mortality, Pub. Health Rep. **69**:1217, 1954.
7. Great Britain. Registrar General: Decennial supplement, England and Wales, 1911. Part 4. Occupational mortality. London, His Majesty's Stationery Office, 1923.
8. Great Britain. Registrar General: Decennial supplement, England and Wales, 1951. Part 1. Occupational mortality. London, Her Majesty's Stationery Office, 1954.
9. Lombard, H. L., and Doering, C. R.: Cancer Studies in Massachusetts. The Relationship Between Cancer and Density of Population in Massachusetts, Proc. Nat. Acad. Sc. **13**:728, 1927.
10. Lombard, H. L., and Doering, C. R.: Cancer Studies in Massachusetts. Cancer Mortality in Nativity Groups, J. Prev. Med. **3**:343, 1929.
11. Mancuso, T. F., Macfarlane, E. M., and Porterfield, J. D.: The Distribution of Cancer Mortality in Ohio, Am. J. Pub. Health **45**:58, 1955.
12. Eastcott, D. F.: The Comparative Mortality Experience From Cancer of Certain Sites Between the Indigenous Non-Maori Population and Immigrants From Great Britain. In Report of the B.E.C.C. (N.Z.) Branch Cancer Registration Scheme, Department of Health, Wellington, New Zealand, 1954.
13. Buechley, R., Dunn, J. E., Jr., Linden, G., and Breslow, L.: Excess Lung Cancer Mortality Rates Among Mexican Women in California. To be published in Cancer.
14. Steiner, P. E.: Cancer: Race and Geography, Baltimore, 1954, Williams & Wilkins Company.
15. Haenszel, W., Moriyama, I. M., and Sirken, M. G.: A Proposed Study for Extending the Scope and Improving the Quality of Mortality Data. Improving the Quality of Statistical Surveys. Washington D. C., American Statistical Association, 1956.
16. Dorn, H. F.: Some Applications of Biometry in the Collection and Evaluation of Medical Data, J. CHRON. DIS. **1**:638, 1955.
17. Cornfield, J.: A Method of Estimating Comparative Rates From Clinical Data. Applications to Cancer of the Lung, Breast and Cervix, J. Nat. Cancer Inst. **11**:1269, 1951.
18. Lombard, H. L., and Doering, C. R.: Cancer Studies in Massachusetts: Habits, Characteristics, and Environment of Individuals With and Without Cancer, New England J Med. **98**:481, 1928.

19. Cutler, S. J.: A Review of the Statistical Evidence on the Association Between Smoking and Lung Cancer, J. Am. Statistical Association **50**:267, 1955.
20. Levin, M. L.: Etiology of Lung Cancer; Present Status, New York J. Med. **54**:769, 1954.
21. Sadowsky, D. A., Gilliam, A. G., and Cornfield, J.: The Statistical Association Between Smoking and Carcinoma of the Lung, J. Nat. Cancer Inst. **13**:1237, 1953.
22. Breslow, L., Hoaglin, L., Rasmussen, G., and Abrams, H. K.: Occupation and Cigarette Smoking as Factors in Lung Cancer, Am. J. Pub. Health **44**:171, 1954.
23. Levin, M. L., Kraus, A. S., Goldberg, I. D., and Gerhardt, P. R.: Problems in the Study of Occupation and Smoking in Relation to Lung Cancer, Cancer **8**:932, 1955.
24. Wynder, E. L., Cornfield, J., Schroff, P. D., and Doraiswami, K. R.: A Study of Environmental Factors in Carcinoma of the Cervix, Am. J. Obst. & Gynec. **68**:1016, 1954.
25. Hammond, E. C., and Horn, D.: The Relationship Between Human Smoking Habits and Death Rates. J. A. M. A. **155**:1316, 1954.
26. White, C., and Bailar, J. C.: Retrospective and Prospective Methods of Studying Association in Medicine, Am. J. Pub. Health **46**:35, 1956.
27. Dorn, H. F.: The Relationship of Cancer of the Lung and the use of Tobacco, American Statistician **8**:7, 1954.
28. Brinton, H. P., Frasier, E. S., and Koven, A. L.: Morbidity and Mortality Experience Among Chromate Workers, Pub. Health Rep. **67**:835, 1952.
29. Mustacchi, P., and Shimkin, M. B.: Occurrence of Cancer in Acromegaly and in Hypopituitarism. To be published in Cancer.
30. Dorn, H. F., and Cutler, S. J.: Morbidity From Cancer in the United States, Public Health Monograph No. 29, 1955. (References to Reports of the Earlier 1937-38 Surveys, Reprints of Which are Almost Impossible to Find, Will be Found in This Monograph.)
31. Haenszel, W., Marcus, S. C., and Zimmerer, E. G.: Cancer Morbidity in Urban and Rural Iowa, Public Health Monograph No. 37, 1956.
32. Patno, M. E.: Geographic Study of Cancer Prevalence Within an Urban Population, Pub. Health Rep. **69**:705, 1954.
33. Dunn, J. E., Jr., Rowan, J. C., Erickson, C. C., and Siegler, E. E.: Uterine Cancer Morbidity Data—Memphis and Shelby County, Tenn., 1950-51, Pub. Health Rep. **69**:269, 1954.
34. Dunn, J. E., Jr., and Sprunt, D. H.: Uterine Cancer Case Finding by Vaginal Cytology, Pub. Health Rep. **70**:341, 1955.
35. Dunn, J. E., Jr.: The Relationship Between Carcinoma in situ and Invasive Cervical Carcinoma, Cancer **6**:873, 1953.
36. Erickson, C. C., Everett, B. E., Jr., Graves, L. M., Kaiser, R. F., Malmgren, R. A., Rube, I. Schreier, P. C., Cutler, S. J., and Sprunt, D. H.: Population Screening for Uterine Cancer by Vaginal Cytology, J. A. M. A. **162**:167, 1956.
37. American College of Surgeons: Manual for Cancer Programs (Approved by Committee on Cancer), Chicago, 1953.
38. Griswold, M. H., Wilder, C. S., Cutler, S. J., and Pollack, E.: Cancer in Connecticut, 1935 Through 1951, Connecticut State Department of Health, Hartford, Conn., 1956.
39. New York State Department of Health, Bureau of Cancer Control, Annual Reports, 1950.
40. Watson, T. A.: Results of Treatment of Cancer in Saskatchewan, 1932-44, Saskatchewan Cancer Commission, Regina, 1951.
41. Watson, T. A.: Incidence of Multiple Cancer, Cancer **6**:365, 1953.
42. Haenszel, W., and Shimkin, M. B.: Smoking Patterns and Epidemiology of Lung Cancer in the United States: Are They Compatible? J. Nat. Cancer Inst. **16**:1417, 1956.

OL.
4
956

DESCRIPTION AND MANAGEMENT OF PARAOSTEOARTHROPATHY IN THE HEMIPLEGIC PATIENT

LEE J. CORDREY, M.D.

CLEVELAND, OHIO

(Received for publication July 7, 1956.)

EXTRA-ARTICULAR ankylosis of joints in malposition is a major complication in the rehabilitation of paraplegic and hemiplegic patients. Any paretic joint may be involved, but one of the most common and most disabling sites of ankylosis is the hip joint. Since 1919, considerable literature has accumulated relative to paraosteoarthropathy in paraplegics, and the pathologic findings have been loosely attributed to myosites ossificans. From our study of the patients presenting this complication, it is believed that these changes primarily represent ossification of the capsule of the hip joint rather than the muscles about it. No reports of paraosteoarthropathy in the hemiplegic patient have been found in the literature relative to this subject.

Eloesser,[4] in 1917, by animal experimentation, was able to demonstrate that in addition to loss of joint sensibility, separate traumata were necessary to produce soft tissue ossification; however, he was unable definitely to establish the mechanism of the pathologic calcification. Dejerine, Ceillier, and Dejerine,[3] in 1919, in a paper presented to the Société de Neurologie in Paris, stated that paraosteoarthropathy in cord lesions has definite sites of predilection with the medial femoral condyle, the first area to be involved, and the hip joints, the second. They found the incidence of these lesions to be 48.7 per cent. Geldmacher,[6] in 1925, noted early formation of para-articular bony layers about hip and knee joints after cord trauma. Frejka,[5] in 1929, stated that development of these areas of bone formation was fully attained within eight months and that the condition then remained static. The mechanism of formation of heterotopic calcification in the human body is not completely known. Wells,[14] in 1925, stated that deposition of calcium salts in areas of tissue degeneration is dependent upon increased alkalinity or decreased carbon dioxide and that these factors may alter solubility products of calcium and phosphate ions, resulting in their precipitation. Vaughn,[13] in 1947, noted that there is a tendency for precipitation of calcium salts to occur when there is a change in the Ph of the media, or when increased phosphatase is present. He noted that precipitation with normal blood levels may take place from noncolloidal ionic solutions. When hypercalcemia is present, precipitation may occur from colloidal solutions of calcium-phosphate-protein complex. Leriche and Policard,[9] in 1926, noted that pathologic calcification can occur in any mesenchymal tissue of low metabolism when its vascularity is further reduced by trauma or infection, and

that the accumulation of edema fluid reduces connective tissue to an embryonic state. This tissue, stimulated by hemorrhage and with local increase in calcium-phosphate salts, is capable of forming bone. None of our patients have manifested the changes typical of Charcot neuroarthropathy and, in many, the joint space has been preserved without evidence of joint involvement per se. In none of these patients has disintegration of the joint occurred. The problem in treatment of these patients has not been instability of the joint, but ankylosis in malposition.

LABORATORY FINDINGS

There has been no significant alteration in calcium, phosphorous, or alkaline phosphatase values in these patients. Serum protein values have been uniformly at the lower limits of normal and there has been no significant change in the A/G ratio. Elevation of blood urea nitrogen values has been present in two of these patients, both of whom had advanced renal disease. Sulkowich determinations have revealed wide variation. These findings are consistent with those reported by other investigators. Chemical changes occurring in the immobilized patient have been well documented by Albright and his associates[1] and are consistent with essentially negative findings noted in this group of patients.

VOL.
4
1956

ROENTGENOGRAPHIC FINDINGS

None of the patients studied had widespread areas of ossification in the thigh muscles, as reported by Miller and O'Neill.[10] The areas of ossification were discrete, confined to the immediate region of the hip joint, and appeared as irregular casts of the joint capsule (Figs. 1 to 4). Dejerine, in her series, observed that the hip joints presented bony bridging in three parts. Anteriorly, an area of ossification extended from the anterior inferior iliac spine to a line between the trochanters. Posteriorly, the calcification extended from the ischium to the posterior border of the greater trochanter. Inferiorly, she noted a more slender bridge of bone arising from the iliopubic region and extending to the lesser trochanter. Radiologically, the pericapsular ossification has the appearance of mature, compact bone. The joint space has been preserved with maintenance of a normal outline of femoral articular surface. In all instances there has been ankylosis of the hip joint in malposition. Osteoporosis of the pelvis and femur has been consistently present.

CLASSIFICATION OF CASES

There are 750 inpatients at Cuyahoga County Hospital for Chronic Disease. The patients presenting neurologic disease involving the lower extremities may be classified as follows: hemiplegics, paraplegics, and multiple sclerotics. There are 103 hemiplegic patients, and of these, 6 have been found to have ankylosis of the involved hip. There are 28 paraplegics, 3 of whom have manifested ossification of the capsule of one or both hip joints. Of 36 multiple sclerotics, only 1 patient has presented hip joint involvement.

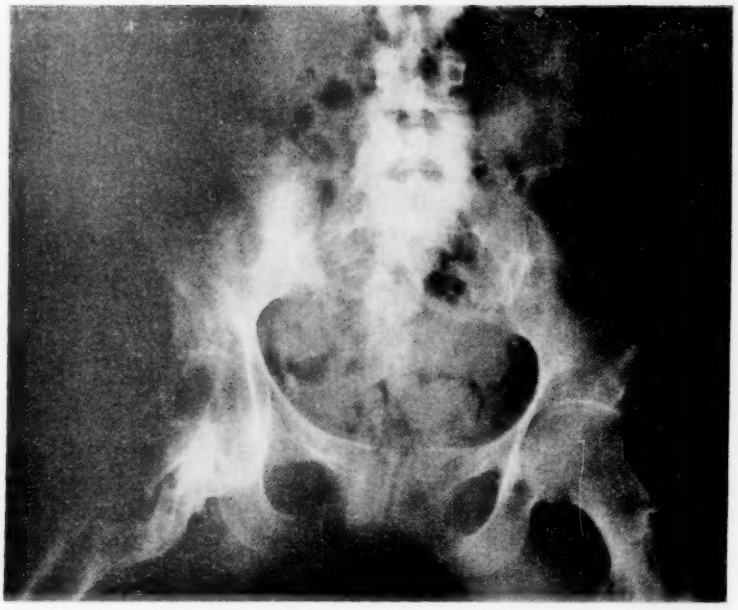


Fig. 1.—Anteroposterior view of the pelvis illustrating bone formation discretely involving the capsule of the right hip joint.

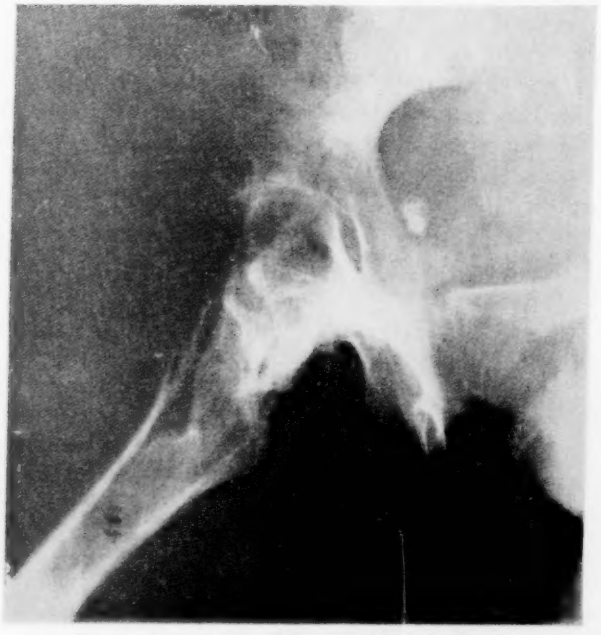


Fig. 2.—Lateral view of the same hip as in Fig. 1.

VOL.
4
1956

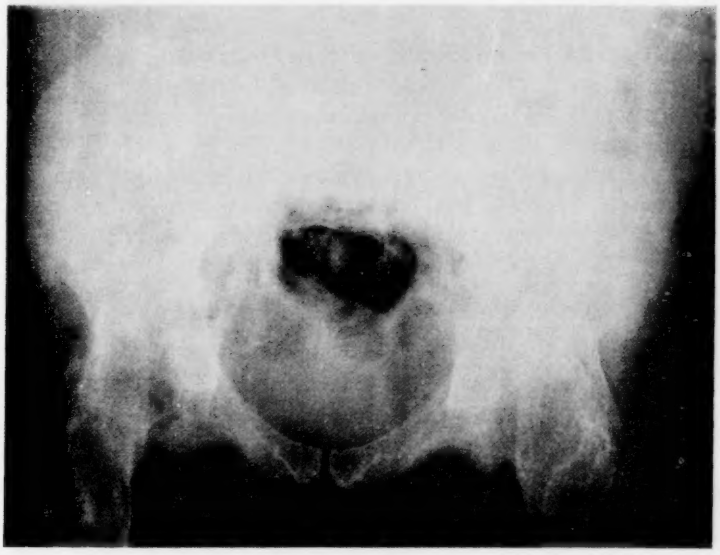


Fig. 3.—A bilateral hemiphegic with involvement of both hips illustrating discrete pericapsular ossification.

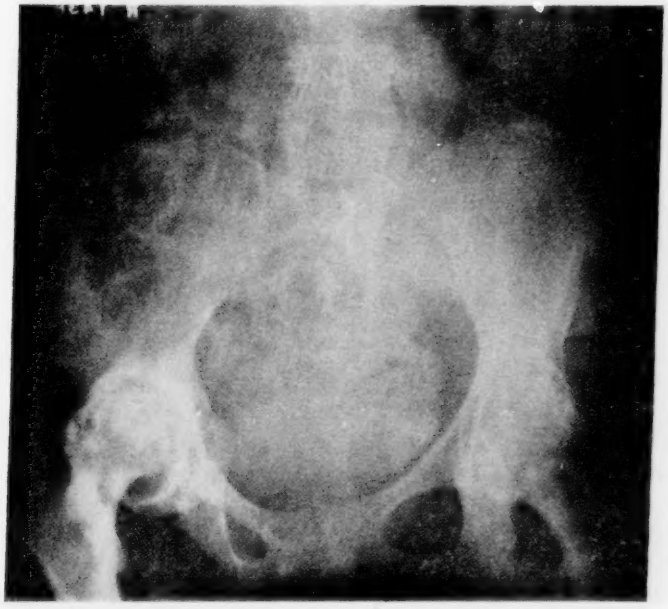


Fig. 4.—Hip in a right hemiplegic illustrating discrete pericapsular ossification with preservation of the joint space.

TREATMENT

Consideration of these patients for active orthopedic measures has been based on two criteria: (1) Would correction of the malposition of the extremity permit ambulation? (2) Would correction of the deformity facilitate nursing care?

All the patients studied presented flexion-external rotation contractures. When the opposite extremity was uninvolved and the patient's general status was such that intensive physical therapy was possible, subtrochanteric osteotomy and

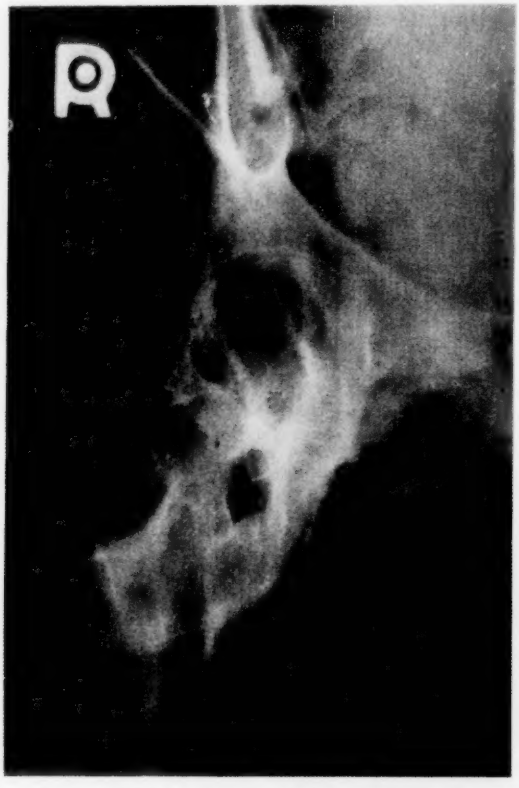


Fig. 5.—X-ray of the hip illustrated in Fig. 1 six months after derotation osteotomy. Patient was permitted weight-bearing at this time.

alignment of the leg in functional position was performed. The first patient operated was relatively young and was immobilized in a one and one-half spica with transfixion pins above and below the osteotomy site. This was considered the safest means of fixation because of the tremendous stress that would be placed at the osteotomy site in the presence of an ankylosed hip (Fig. 5). The general status of the second patient operated precluded lengthy immobilization, however, and fixation of the osteotomized femur was achieved with a Smith-Peterson nail and Thornton plate (Fig. 6). This patient was placed in a wheel chair on her third postoperative day; in the sixth postoperative week, standing

in a tilt table was instituted without attendant difficulty. Subsequent patients have been treated by this method without complications and without the necessity of the intensive nursing care entailed by use of plaster immobilization. When ambulation is begun, the involved extremity is fitted with a long leg brace with an automatic knee lock and Klenzak ankle. Gains in ambulation are limited, but the patient is afforded a measure of independence totally lacking before correction of the malposition.

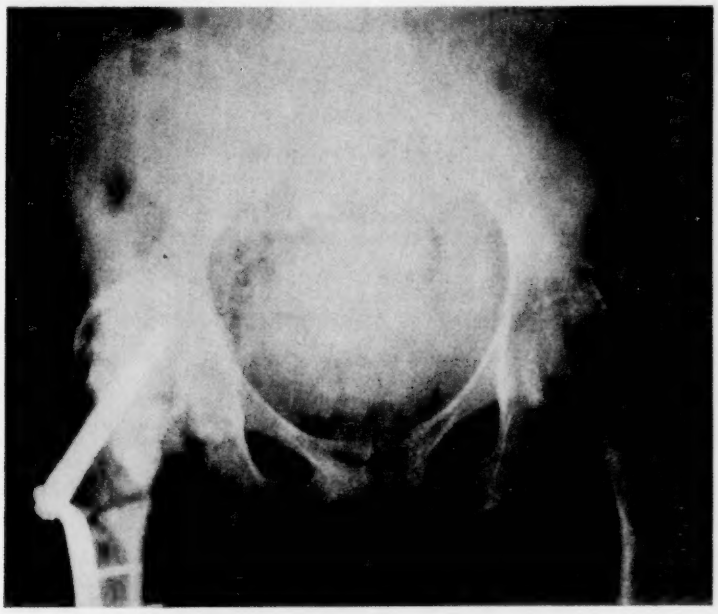


Fig. 6.—X-ray four weeks postoperative demonstrating correction of the adduction-rotation deformity. Patient ambulated three months after surgery.

Inspection of the hip at surgery revealed the areas of ossification to be composed of mature, dense bone which had undergone complete fusion with femur and ilium without evidence of a zone of transition. There was no evidence of infiltration of the surrounding muscles with calcific deposits, and a normal periosteal layer which could be stripped away easily, permitting reflection of overlying muscle, was present. The surrounding muscle was edematous, yellow-brown in color, and without evidence of contractile power.

SUMMARY

Paraosteoarthropathy is a relatively uncommon complication which may occur about the hip in any neurologic disease producing paralysis and diminished sensation of the lower extremities. It has not hitherto been reported in the hemiplegic patient. No evidence was found to indicate that there was primarily involvement of the muscle, and the capsule of the hip joint in these patients was discretely ossified. The etiologic factor, as suggested by other investigators, is

believed to be frequent, low grade traumata to the paretic hip joint with tearing of the unprotected capsule followed by hemorrhage, degeneration, calcification, and ossification. Proper splinting of the involved extremity and gentle manipulation by nursing attendants and physical therapists is indicated at all times in the treatment of patients with paralyzed extremities if this complication is to be prevented. When there is ankylosis of the hip joint of a nonfunctioning extremity in malposition, subtrochanteric osteotomy of the femur, alignment in functional position, and internal fixation has proved a simple, successful method of treatment. If the opposite extremity is uninvolved, limited ambulation can be achieved.

REFERENCES

1. Albright, F., and Reifenstein, E. D., Jr.: The Parathyroid Glands and Metabolic Bone Disease, Baltimore, 1948, Williams & Wilkins Company.
2. Brailsford, James F.: Changes in Bone, Joints and Soft Tissues Associated With Disease of Injuries of the Central Nervous System, Brit. J. Radiol. **14**:320, 1941.
3. Dejerine, Ceillier, Dejerine: Para-osteo-arthropaties des paraplegiques par lesion medullaire, etude anatomique et histologique, Rev. neurol. **32**:399, 1919.
4. Eloesser, L.: On the Nature of Neuropathic Affections of the Joints, Ann. Surg. **66**:201, 1917.
5. Frejka, B.: Heterotopic Ossification and Nyositis Ossificans Progressiva, J. Bone & Joint Surg. **11**:157, 1929.
6. Geldmacher, M.: Beitrag zu den Parartikularen Verknocherungen nach Querschnittslasion des Ruckenmarks, Deutsche Ztschr. f. Chir. **191**:180, 1925.
7. Hielburn, N., and Kuhn, W. G., Jr.: Erosive Bone Lesion and Soft-tissue Ossification Associated With Spinal Cord Injuries (Paraplegia), Radiology **48**:579, 1947.
8. Koltz, O.: Studies Upon Calcareous Degeneration, I. The Process of Pathological Calcification, J. Exper. Med. **7**:632, 1905.
9. Leriche and Policard: Les problemes de la physiologie normale et pathologique de l'os, Paris, 1926, Masson & Cie.
10. Miller, L. F., and O'Neill, C. J.: Myositis Ossificans in Paraplegics, J. Bone & Joint Surg. **31**-*A*:283, 1949.
11. Soffer, L. J., and Cohn, C.: Primary and Secondary Hyperparathyroidism, Arch. Int. Med. **71**:630, 1943.
12. Soule, A. B.: Neurogenic Ossifying Fibromyopathies, A Preliminary Report, **2**:485, 1945.
13. Vaughn, J. H., Sosman, M. C., and Kinney, T. D.: Nephrocalcinosis, Am. J. Roentgenol. **58**:33, 1947.
14. Wells, H. G.: Chemical Pathology, ed. 5, pp. 486-504.

VOL. 4 195

Review

PRESENT-DAY MANAGEMENT OF TUBERCULOSIS

ROGER S. MITCHELL, M.D.

DENVER, COLO.

From the University of Colorado School of Medicine and the Colorado Foundation for Research in Tuberculosis, Denver, Colo.

(Received for publication August 10, 1956.)

RECENT important advances are causing continuing changes in the management of tuberculosis. There will surely be further important refinements of present-day methods, even without the discovery of major new weapons. This review may be regarded, therefore, as a progress report on knowledge of the therapy of tuberculosis in 1956.

In order to understand more fully the disparity of present attitudes on this subject, one should have a broad picture of the evolution of tuberculosis during the past fifty years. Authorities agree that long before we had anything approaching specific therapy for the disease, there was a slow but steady decrease in the incidence of and mortality from the disease throughout the world.[1] This was countered by the observation that the case fatality rate showed very little change over a period of twenty years between 1921 and 1941.[2]

There is no question, on the other hand, that over-all mortality and case fatality rates have been abruptly and materially reduced since the introduction of truly effective, prolonged, multiple chemotherapy in 1950-1951.[3] The 1954-1955 tuberculosis mortality in the United States was about 10 per 100,000 persons compared to over 20 in 1949 and over 200 at the turn of the century. Another change is the tendency for tuberculosis now to involve predominantly persons over 40 years of age, particularly males. Extrapulmonary tuberculosis is less frequent, though this is not to be traced to the control of bovine tuberculosis as popularly supposed, but to some as yet undefined factor.[4]

IMPROVEMENTS IN DIAGNOSIS

Successful therapy is clearly dependent upon accurate diagnosis. For the enlightened clinician it is becoming increasingly difficult to make an unquestioned diagnosis of tuberculosis, not only because of the reduced frequency of

the disease but also because of improved bacteriologic techniques and new knowledge of diseases which can mimic tuberculosis.

Attention has recently been drawn to a tuberculosis-like disease caused by atypical mycobacteria which are acid-fast and easily mistaken for tubercle bacilli on smear.[5] On routine media used to culture tubercle bacilli they grow out rapidly (in 5 to 10 days instead of 14 to 45); their colonies are frequently orange or yellow, often only after exposure to light. They are usually smooth, usually do not form cords, are usually neutral red positive, and are not completely susceptible to antituberculous drugs; in fact, resistance to para-aminosalicylic acid is sufficiently notable to aid in their identification. Their animal pathogenicity differs from that of true tubercle bacilli, particularly in that they are nonpathogenic for the guinea pig.[6] These atypical mycobacteria have been recognized for many years, but increased attention has been paid to them because of the recent realization of their human pathogenicity.[5] There are also many acid-fast saprophytes which may be found in gastric washings, tap water, and elsewhere, whence they may get into specimens and cause confusion in the unwary laboratory.

Nocardia or *Actinomyces asteroides* are microorganisms intermediate between true fungi and true bacteria. They are aerobic, gram-positive, and weakly acid fast. Though they multiply in filaments, these are often broken into rod-shaped bodies indistinguishable from tubercle bacilli on smear.[7] The disease nocardiosis is most apt to involve the lungs, lymph nodes, and meninges.[8]

Certain fungus diseases, particularly histoplasmosis,[9] and to a lesser extent coccidioidomycosis,[10] can resemble chronic pulmonary tuberculosis, including the findings of pulmonary cavitation and fibrosis. These diseases may coexist with each other and with tuberculosis.[11] Sputum bacteriology and fungus skin tests and serologic tests are most helpful in distinguishing these diseases, but are not completely reliable. Sputum bacteriology may be definitive if positive, but techniques are fussy and growth is not always easy to obtain. In short, the differential is often difficult.

An area of bronchiectasis surrounded by an area of pneumonitis may be indistinguishable from tuberculosis. Lung abscess is actually more apt to occur in an upper than in a lower lobe. Perhaps most important, data from many clinics have amply demonstrated that primary carcinoma of the lung may mimic tuberculosis of the lung or bronchus. Even flecks of calcium within an abnormal lung shadow do not exclude cancer,[12] although their coexistence is rare.

The diagnosis of tuberculosis hinges finally upon the tuberculin test and repeated bacteriologic examinations, including microscopy, culture, and at times, animal inoculation. In the case of pulmonary tuberculosis, one almost always finds an abnormal roentgenographic shadow, particularly in the upper posterior lung fields. Cavitation in these areas still more strongly suggests but does not necessarily confirm the diagnosis. A history consistent with the disease may or may not be present.

Diagnostic procedures which may be necessary in order to elucidate these cases include bronchoscopy; pulmonary angiography; peripheral lymph node, scalene fat pad, pleural or direct lung biopsy; tuberculin and fungus skin tests;

and routine and special roentgenography including fluoroscopy, tomography, and oblique and apical lordotic projections.

Reactions only to 10 mg. old tuberculin (0.1 c.c., 1:10 dilution O.T., or 1,000 T.U.) or second strength P.P.D. (0.005 mg. or 250 T.U.) are considered nonspecific. Intermediate strength P.P.D. (0.0001 mg. or 5 T.U.) is recommended as the most reliable criterion of tuberculin hypersensitivity.[13]

In using the scalene fat pad biopsy it should be stressed that lesions throughout the right lung drain to the lymphatics on the right, those in the upper half of the left lung drain to the left, those in the lower middle fourth of the left drain to either side, and lesions in the lower fourth of the left lung usually drain to the right.[14] This is obviously important in deciding which side of the neck to explore.

The therapy of tuberculosis will now be discussed under the headings chemotherapy, patient education, special therapy applicable only to pulmonary tuberculosis, including especially collapse and pulmonary resection, special comments regarding the therapy of extrapulmonary tuberculosis, association of tuberculosis with other major diseases, and the results of modern therapy.

VOL.
4
956

CHEMOTHERAPY OF TUBERCULOSIS

Standard agents.—There are three principal antibacterial agents with which to treat tuberculosis. In the order of their effectiveness they are isoniazid (INH), streptomycin (SM)-or dihydrostreptomycin (DHSM), and para-aminosalicylic acid (PAS). The dosage of these drugs is shown in Table I.

TABLE I. DOSAGE AND ROUTE OF ADMINISTRATION OF THREE PRINCIPAL ANTITUBERCULOSIS DRUGS

DRUG	SYMBOL	ROUTE OF ADMINISTRATION	DOSAGE RANGE IN MG./KG. OF BODY WEIGHT	RECOMMENDED DOSAGE*
Isoniazid	INH	Oral	3-20 in 2 or 3 daily doses	10 mg./Kg./day
Streptomycin or Dihydrostreptomycin	SM DHSM	I.M.	7-20 once daily 2-7 days/wk.	2-7 Gm./week
Para-aminosalicylic acid	PAS	Oral	200 in 3 daily doses	15.5 Gm. Sod. salt (or 12 Gm. acid/day)

*Dosages recommended by author.

INH and PAS may be given parenterally to unconscious patients, although gavage is possible and may be preferable. Intravenous PAS is used with minimum toxicity and minimum damage to veins and with apparent good effect in many parts of the world outside the United States.[15] Intrathecal SM has been used in meningitis but is no longer deemed necessary or advisable. There is no uniform agreement on dosage. Daily SM is probably more effective than twice weekly, although in combination with PAS the superiority of daily SM has not been demonstrated in trials on large numbers of patients treated and observed for 12 to 18 months.[16] Daily SM has been shown to be more effective than

twice weekly SM with small (i.e., 200 mg./day) doses of INH, but this study would have been more convincing if none of the patients admitted to the study had had prior chemotherapy.[17] Daily SM-INH was somewhat superior to INH-PAS in the same study, but this comparison suffers somewhat from both the selection of patients and the low dosage of INH.[17] PAS dosage with INH apparently may be less than with SM.[18]

INH dosage is still a highly controversial matter. There is some recent evidence that 10 mg./Kg./day is the best dose: blood concentrations of biologically active INH rise as the dosage is raised to this level but fail to go much higher as the dosage is doubled or tripled beyond that. The levels of total INH (measured chemically by the Kelly-Poet method) are, on the other hand, roughly a function of dose.[19] Clinical trials, however, indicate that a dose of 3 mg./Kg./day is as effective as 10 mg./Kg./day.[18]

INH and PAS Metabolism.—Judging from the proportions of free INH and its metabolites recovered from the 48-hour urine, INH is inactivated to a widely variable degree in man.[20-22] Most of the metabolites, 30 to 60 per cent of which are acetylated forms, have essentially no antituberculosis effect. Furthermore, the marked individual differences in the rate and pattern of inactivation remain unchanged despite changes in nutrition and general health and the passage of time.[22] Clinical effectiveness and incidence of neuritis both rise with rising free INH urine levels.[23] Tissue levels of $C^{14}INH$ are often higher than blood levels[24]; this may explain the apparent benefit from INH in some patients with very low blood levels of biologically active INH. The biologic activity of INH in the tissues, however, has not yet been determined.

Recently, it has been learned that the concurrent administration of PAS will frequently raise the levels of biologically active INH in the blood of humans, especially when they are low on INH alone.[25-27] In practice, the situation is somewhat as follows: some patients on a daily dose of 3 to 5 mg./Kg. INH (the customary 300 mg. daily dose) without PAS will have at least 0.8 mcg. of biologically active INH/ml. of blood serum 6 hours after the administration of one-third of the daily dose (i.e., "slow inactivation"); others will have a "rapid" inactivation on this dose (i.e., less than 0.4 mcg./ml. at 6 hours) or "intermediate" inactivation (0.4 to 0.6 mcg./ml.). Still others on this dose will have 0.8 mcg. 6-hour levels only with the addition of PAS, or require 10 to 16 mg./Kg./day of INH without PAS. There are a few patients who attain good levels of biologically active drug only with PAS plus 10 to 16 mg. INH/Kg./day. Finally, there are the rare individuals in whom an 8 mg./Kg. test dose of INH, plus PAS, has failed to yield more than 0.4 mcg./ml. of biologically active INH at 6 hours.[19] In short, PAS seems to have a dual role in INH-PAS therapy, both as an antituberculosis agent and as an INH (biologically effective) sparing agent.

This phenomenon of raising effective INH levels with PAS is tentatively explained on the basis of competition for acetylation.[25] This may be so since a 3 Gm. dose of para-aminobenzoic acid, which is also partially metabolized by acetylation, has caused a rise in biologically active blood INH in patients also having a rise with PAS.[28]

In short, until we have a practical chemical test which accurately reflects the metabolic fate of INH in the individual, and the effect of PAS thereon, it

is my conviction that INH should be given in a dosage of 10 mg./Kg./day, and always with PAS. As INH dosage is increased above the 10 mg./Kg. dosage, the risk of neuritis and the pyridoxine requirement (see below) also increase without a significant gain in biologically active INH blood levels.

There has been interesting support for this concept in the finding that patients with rapid INH inactivation tend to continue excreting INH-susceptible tubercle bacilli if cultures remain positive after several months of INH therapy.[19,27,28,29] This strongly suggests deficient delivery of biologically active INH to the bacilli.[29] Contrariwise, patients with slow INH inactivation and with cultures still positive after several months of INH therapy tend to excrete INH-resistant *Myco. tuberculosis.*

These observations clearly need further confirmation and elaboration. Meanwhile, they provide nice support to the clinical trials which have shown a superiority of daily INH-PAS over SM twice weekly-daily INH in far-advanced pulmonary tuberculosis.[30,31]

Since PAS is metabolized (and inactivated) largely by acetylation and in about the same degree as INH in humans,[32] it is quite possible that some failures of SM-PAS therapy may be attributable to inadequate PAS (or essentially single drug [SM]) therapy.

Mode of Action.—The mode of action of these drugs is not well understood. They penetrate freely into cerebrospinal fluid[33] and into caseous tissue.[24] They act almost exclusively upon actively multiplying organisms in vitro and presumably also in the human host. Under these conditions, their action is predominantly bactericidal[34]; this is more true of INH than of SM and PAS.[35] There is much to suggest that these drugs act by interfering with essential enzyme systems of the bacilli, thus killing the organism or interfering with its ability to multiply, or increasing its susceptibility to natural bactericidal agents in the host.[36]

There is indubitable evidence that two drugs are more effective than one against human tuberculosis.[37] This is largely due, it is thought, to the lesser chance of bacterial mutation to strains resistant to two drugs. By the same reasoning, three agents should be more effective than two.

Toxicity.—All of these drugs have some toxicity. SM and DHSM may cause dizziness or deafness by involvement of the eighth cranial nerve. Dizziness is more common with SM, and deafness with DHSM; only a small proportion of patients is so affected. This phenomenon has considerable relationship to the total amount of drug administered; thus the patient receiving 1 Gm. twice weekly will develop toxic effects later and with less frequency than the patient receiving 1 Gm. a day for the same period of time.[38] Two grams of SM daily will increase the risk still more. SM and DHSM toxicity are also related to blood levels. This may be partially circumvented without loss of effectiveness by the administration of equal portions of SM and DHSM (i.e., streptoduocin).[39] Probably for the same reason, toxicity is more common in patients with renal insufficiency and in older patients. Previously impaired renal function may also be aggravated by SM and DHSM at times.

The principal toxicity of INH is a severe peripheral neuritis characterized by pain and paraesthesiae without striking physical findings. This again ap-

pears to be related to total or cumulative dosage. The concurrent administration of 50 to 200 mg. of pyridoxine (vitamin B_6) daily will prevent this serious complication.[40] It also should be stressed that pyridoxine has little curative effect on the established neuritis. Some episodes of acute psychosis have occurred during INH therapy, though there is doubt about a causal relationship.[41] Iproniazid, the isopropyl derivative of INH, has been clearly associated with numerous instances of acute psychosis and other major toxicity and has now been practically abandoned.[42,43]

The principal toxicity of PAS is gastrointestinal intolerance. This is more likely to occur in the aged and in the clinically ill patient than in the young or mildly ill patient.[44] This troublesome problem occurs in from 10 to 50 per cent or more of all patients on the drug. It appears to be related principally to the quality of the drug, which in turn is influenced by its age, presence of impurities, and its exposure to light, heat, moisture, and heavy metals. If the drug reveals any discoloration in solution, there is an increased risk of toxicity and probably some loss of antituberculous effect.[45] Another danger with sodium PAS is in patients with cardiac decompensation, especially those with chronic cor pulmonale. These patients usually are greatly improved by sodium restriction and consequently react very poorly to the large amount of sodium in the customary doses of sodium PAS; acid PAS is a satisfactory substitute. PAS also has a goitrogenic effect in a limited number of individuals; administration of iodine tends to minimize this effect during continued PAS administration; there is usually a prompt return to normal after the drug is discontinued.[46] Serious liver toxicity has also been reported.[47]

All three drugs may give rise to hypersensitivity reactions which can be extremely hazardous and, rarely, even fatal. This is most commonly noted with PAS, but has been traced to each of the other drugs, sometimes to two drugs at once. There is no great risk if one is alert to the possibility of hypersensitivity, if the drugs are stopped and resumed very gingerly, being on the lookout for recurrence of symptoms, especially fever. Occasionally, slow careful desensitization will prevent recurrence of hypersensitivity, starting with doses as low as 1 mg. INH or SM and 10 mg. PAS, doubling the dose every 3 days and taking 4 to 6 weeks to complete the desensitization. Antihistaminic drugs may help in mild cases; cortisone in full doses is very effective in suppressing hypersensitivity but must be continued for long periods in order to maintain protection. If exfoliative dermatitis should occur or be imminent, however, the responsible drug should be permanently withdrawn and not be repeated even with steroid coverage.

Bacterial Resistance to Drugs.—The emergence of bacterial resistance to each antituberculosis drug now in clinical or experimental use has been described. There is no longer any doubt that this is the result of spontaneous mutation accompanied by the selective reduction of the drug-susceptible population upon the exhibition of the drug.[48,49]

The clinical usefulness of drug susceptibility tests is regarded by some as important and by others as relatively useless. Contributing to this confusion is the fact that there is still no agreement on a correlation between the concen-

tration of drug in culture medium which just inhibits the growth of tubercle bacilli on the one hand, and clinical failure to respond to the drug in the human patient on the other. The most popular dividing line between susceptibility and resistance for SM is 10 mcg./ml.,[50] but some authorities feel this should be as low as 2.5 mcg./ml.[36,51,52] In the case of PAS the usual concentration is 10 mcg./ml.,[50] but others feel that this should be as low as 2 to 3.5 mcg./ml.[51,52] PAS-susceptibility tests are notoriously difficult to perform,[36] probably because of the rapid deterioration of PAS in solution. In the case of INH the concentrations recommended range from 10 to 1, usually 5 mcg./ml.[50]; some authorities now feel that the dividing line should be as low as 0.2 mcg./ml.[36,51,52,53]

To be complete, a test reporting drug resistance should include an estimation of the proportions of the bacterial population obtained from the patient which show the various degrees of resistance or susceptibility. The amount and speed of growth on drug-containing media should also be compared with the growth in the nondrug-containing control. It is my opinion that when the drug susceptibility test is performed, reported and interpreted with care, and the low levels of division between resistance and susceptibility, mentioned above, are used, there is excellent correlation between the findings in the laboratory and in the clinic with regard to SM and PAS.[54] Clinical response to INH in the presence of INH resistance, on the other hand, is variable[55] and in fact severe progressions of disease under these circumstances seldom occur.[56] The generalization may also be made that the greater the degree of in vitro resistance, the less clinical response may be anticipated in vivo.

INH-resistant tubercle bacilli may be subdivided into two general categories: the INH-highly-resistant, catalase-negative strains, and the INH-mildly-resistant, catalase-positive strains.[58] After administration of INH for several weeks or more, patients usually excrete populations of organisms predominantly, occasionally entirely, characterized in one of these two ways; a few continue to excrete the "wild" INH-susceptible, catalase-positive strain present prior to therapy.[59] When INH is used in high dosage (i.e., 10 mg./Kg./day or more) there is an increased chance that INH-resistant mutants which may appear will be the highly resistant catalase-negative variety.[52] The INH-mildly-resistant, catalase-positive mutants are usually as pathogenic for man and animals as are the parent INH-susceptible "wild" strains. The INH-highly-resistant, catalase-negative strains, however, appear to have a reduced *but not absent* pathogenicity and virulence for laboratory animals[58,60] and for man.[57]

The chance of resistance to all of the drugs increases as time on each drug passes, particularly in those patients who continue to excrete *Myco. tuberculosis*. The chance of SM resistance is closely related to the presence and size of cavities,[18,61] to the persistent excretion of bacilli during chemotherapy,[18] and to the confluence of shadows.[62] The same appears to be true of PAS, INH, and the other antituberculosis drugs.[18,45]

While there are exceptions, INH resistance is the most common and earliest to appear, SM resistance intermediate, and PAS resistance the least frequent and slowest to make its appearance.[45,63]

Thus the serious complication of the emergence of drug resistance can often be anticipated from the age and roentgenographic character of the disease at

the outset of treatment. In these cases, therefore, an indicated pulmonary resection should be performed early, in order to be assured of competent drug coverage; cavities should be closed by temporary or permanent collapse as early as feasible, if they cannot or should not be resected, in order further to reduce the risk of the emergence of drug resistance. Resection will be covered in more detail later.

It is important to stress that when in vitro resistance to an agent appears, this agent need not necessarily be stopped for one or more of the following reasons: (a) unless the laboratory specifically states that all the organisms obtained from the host are resistant, there may well be some susceptible organisms in the specimen; (b) not all organisms in the host may be available for study in even a series of specimens; (c) there is no known harm from such treatment, such as might result from drug dependence; (d) resistance specifically to INH does not preclude additional benefit from that drug.[56]

From the first discovery that drug resistance played an important role in the chemotherapy of tuberculosis, there has been fear of a rising incidence of new tuberculosis caused by drug-resistant bacilli.[64] In a survey of admissions to Veteran's Administration hospitals in 1951-1952, the frequency of primary SM resistance was 3.1 per cent.[65] More recently in a survey of 385 newly diagnosed cases made between July, 1953, and January, 1955, 11 per cent showed some evidence of resistance to SM or INH, but only 1.6 per cent showed "significant" resistance to SM and 2.3 per cent "significant" resistance to INH.[66] Since very low levels of drug resistance may have clinical significance, the rise from 3.1 per cent to 11 per cent may be regarded as disturbing. It is also the rule that once tubercle bacilli are drug resistant, reverse mutation to susceptibility does not occur,[67] although the possibility that this may have occurred in tuberculous monkeys was mentioned recently.[60]

Regimens.—Numerous regimens have been devised and tried under controlled conditions.[16-18,30,31] The ones in most frequent use in the United States are:

a. SM 1 Gm. twice weekly, PAS 12 Gm. daily
b. SM 1 Gm. twice weekly, INH 300 mg. daily
c. INH 300 mg. daily, PAS 12 Gm. daily
d. SM 1 Gm. twice weekly, INH 300 mg. daily, and PAS 12 Gm. daily

Of these, the INH-PAS combination appears to be the most effective two-drug combination.[19,30,31]

It should be stressed that while there may be no detectable differences in roentgenographic clearing or worsening, cavity closure and reversal of infectiousness in large groups of patients during twelve to eighteen months of treatment and observation, relapse experience over the ensuing five years or so may reveal differences between regimens, especially in the very advanced cases. In the severe case in particular, therefore, it is my opinion that *daily* administration of all drugs, including SM 1 Gm., 1NH 10 mg./Kg., and PAS 12 Gm., may prove to be the most effective combination of these three agents.

There are other drugs of more than passing interest in the treatment of tuberculosis which are listed with their dosage and mode of administration in

Table II. All of these drugs have a well-demonstrated antituberculosis effect in vitro as well as in vivo.

TABLE II. SECONDARY ANTITUBERCULOSIS DRUGS

DRUG	ROUTE OF ADMINISTRATION	ADULT DOSAGE
Pyrazinamide	Oral	25-50 mg./Kg./day
Viomycin	Intramuscular	1-2 Gm. twice a week
Oxytetracycline and tetracycline	Oral	1-5 Gm./day
Cycloserine	Oral	250 mg. twice daily

Viomycin is not a very effective drug, falling roughly midway between SM and PAS as a single drug, but much less effective as a companion drug to SM and INH than PAS. It has been used with some success to treat exacerbations of disease or in covering major surgical intervention in cases with clinical or laboratory evidence of resistance to the other drugs. The toxicity of viomycin is minimal on the 1-2 Gm. twice weekly dosage schedule. On higher doses most patients sooner or later experience liver and renal toxicity, often severe, and evidence of electrolyte imbalance manifested particularly by tetanic convulsions.[68]

Pyrazinamide alone has proved highly effective, even in advanced disease resistant to other drugs, for brief periods of about 30 days, sometimes longer. It may therefore be used effectively to cover excisional surgery, but only when carefully timed.[69] The limiting factor is the rapid emergence of clinical resistance, especially when it is used in unfavorable cases. Following animal experiments[70] it has been found, however, that pyrazinamide-INH works exceedingly well in humans who *never received either drug before*, and in fact may be as effective a combination as we have to date.[71] A possible explanation for this combined effect is the observation that *Myco. tuberculosis* organisms resistant to between 5 and 15 mcg. of INH/ml. of medium are susceptible to pyrazinamide whereas both INH-susceptible organisms and those resistant to more than 15 mcg. INH/ml. of medium are resistant to pyrazinamide.[72] It is also known that pyrazinamide, in contrast to PAS, is not predominantly metabolized by acetylation and does not raise free INH blood levels.[19] A serious drawback to the widespread use of pyrazinamide is the risk of toxic hepatitis; this has occurred in about 10 per cent of cases, with clinical jaundice seen in about 3 per cent.[73] This problem can be minimized by lowering dosage from 40 to 25 mg./Kg./day, by withholding the drug if liver function tests are significantly abnormal, and by abandoning it if they show deterioration.[18,50] There have been some reported deaths from pyrazinamide, but most of these patients had continued therapy after the onset of clinical jaundice.[74]

Oxytetracycline and *tetracycline*, like PAS, are only mildly antituberculous alone, but act by preventing or delaying the emergence of resistance to SM in doses of 1-2 Gm./day[75] and to INH in doses of 5 Gm./day.[76] Intolerance manifested by gastrointestinal upset, especially diarrhea, is the major toxicity encountered.

Cycloserine is currently under investigation and has not yet been recommended for general use. It appears to work particularly well in combination with INH in both experimental animals[77] and in man.[78] It has been disappointing in the treatment of far-advanced pulmonary tuberculosis no longer responsive to the action of the standard drugs[78,79]; this type of case, however, is a very severe test of any agent. In fresh favorable cases of pulmonary tuberculosis cycloserine has a satisfactory effect. The principal toxic manifestation of cycloserine is convulsions; these are apparently related to the size of the individual dose and to blood levels of the drug.[79]

What is our *best regimen* today from every angle? In summary, all three drugs daily in full doses appear best on theoretical grounds. There is evidence that SM twice weekly appears to add nothing to INH-PAS and INH-PAS is better than SM twice weekly with INH and SM-PAS. Daily SM-INH has not been conclusively compared with INH-PAS as yet but is better than SM twice weekly with INH. There is evidence that unless blood or urine determinations for free INH can be made, INH should not be given without PAS unless a suitable substitute for PAS is found.

Retreatment.—The patient who has had some prior chemotherapy, often for short or interrupted courses, is a common practical problem. The following general statements may be made regarding the *re*treatment of these patients:

A. Be sure to give the 3 major drugs (SM, INH, and PAS) a thorough trial before relying upon the secondary drugs (pyrazinamide, viomycin, oxytetracycline, tetracycline, and cycloserine).

B. Always give serious consideration to the use of INH in any retreatment regimen regardless of any consideration except serious toxicity, since patients with INH resistance who receive INH do not show the deterioration so commonly seen in comparable situations with the other drugs.

C. In patients who are clearly failures of prolonged SM-PAS therapy and who have never had INH or pyrazinamide, INH-pyrazinamide is strongly recommended, provided liver function is good and liver function tests are readily available throughout the course of treatment.

D. Save at least one effective agent to cover resectional surgery if this can be anticipated in the foreseeable future.

E. It is frequently impractical to await the outcome of in vitro drug susceptibility tests. Therefore, if a patient has received two or all three of the major drugs before, give these three in maximum dosage daily and readjust therapy later as response to treatment, toleration, and drug susceptibility tests may indicate.

F. If only one of the 3 major drugs has been used, and for long enough to make the emergence of resistance likely, use the other two.

Indications.—There is general agreement today that any case of tuberculosis active by any reliable criterion in any part of the body should receive chemotherapy.

Some observers feel that regimens may be individualized on the basis of severity of the lesion and other considerations.[80] It is agreed that meningitis and very advanced lesions elsewhere may be classed as "panic" cases and so

treated; it is not agreed that "mild" situations can reliably be sorted out from the "moderate" ones.

There is still some disagreement as to whether an individual with known recent onset of tuberculin hypersensitivity, without any other evidence of tuberculosis, should be treated. In favor of its use is the fact that chemotherapy should prevent the serious complications of new infection, particularly miliary tuberculosis, meningitis, and the progressive primary infection so apt to occur in the first few years of life. If significant clinical tuberculosis is likely to occur in 1 or 0.1 per cent of a given group of recent converters, the use of effective essentially nontoxic chemotherapy to all of the group appears sound. On the other hand, there are theoretical disadvantages. We do not know whether the organisms are multiplying rapidly in such a case, hence we would not know whether the drugs will attack the infecting organisms. Furthermore, there is the possibility that the use of drugs before the onset of acquired host resistance—implied, but not proved by tuberculin hypersensitivity—may fail to control the disease and at the same time encourage the emergence of drug resistance. Chemotherapy alone can seldom if ever effect a cure of tuberculosis; this clearly requires the help of host factors which we call "resistance" or immunity—factors which help to wall off and even kill the parasites. There is a natural reluctance to treat 100 or 1,000 individuals in order to catch the one who really needs it. The toxicity of the agents used cannot completely be disregarded. Even apparent early success will not prove that the final result will be desirable since it may be several years before a definitive answer will be available.

In regard to the therapy of the recent converter, therefore, I am left with an open question, to be answered finally only by clinical trial. The vast majority of published opinions today favor treating all recent converters up to 3 or 4 years of age and any recent converter in a heavily exposed, highly unfavorable environment. Treatment of the less threatened individuals might better be withheld until the outcome of controlled trials now under way becomes known.[81]

Interruptions.—In the early years of the specific chemotherapy of tuberculosis, short "courses" of both single and multiple drugs were tried, often with satisfactory initial improvement, but with disappointing late results. It has also been shown that interruptions of SM-PAS therapy impair results, apparently by increasing the risk of drug resistance.[54] The same is presumed to be true of INH regimens, but with no clear substantiation as yet. If interruption is unavoidable it therefore appears wise to stop both drugs of a two-drug regimen since the administration of a single drug encourages the emergence of drug resistance. If desensitization to one drug is indicated, small desensitizing doses of both drugs simultaneously appear to me to be indicated on the basis of this reasoning. If one of two drugs must be stopped and not resumed for some reason, another appropriate one should be substituted. This practice of substitution is widespread, often without sufficient justification, apparently on the basis that all is well if any two drugs are given. Until more data are available, it seems best to maintain the regimen selected until there is insurmountable and severe toxicity or unmistakable clinical indication of failure to respond to the agents being used.

Duration.—The answer to the question of duration of chemotherapy is not yet known. We know on the basis of early relapse rates that less than twelve months of uninterrupted original chemotherapy is not enough for many patients.[54] We know that the patients with extensive chronic disease, especially those with a cavity of 4 cm. or more in diameter, need much longer therapy than those with mild or fresh lesions, especially those without cavity. We also know that patients receiving retreatment, especially those with any evidence of drug resistance, are apt to need much more than those on original treatment. Using these modifying principles, the schedule shown in Table III may be regarded as a general guide based upon our present state of knowledge.

TABLE III. RECOMMENDED DURATION OF ORIGINAL UNINTERRUPTED CHEMOTHERAPY

EXTENT OF DISEASE	RECOMMENDED DURATION OF THERAPY*
Minimal	12-18 mos.
Moderately advanced	15-24 mos.
Far advanced	18-36 mos.

*Provided the patient has attained the inactive state as defined by National Tuberculosis Association Diagnostic Standards (1955) at least 6 months or more before terminating therapy.

This table omits from consideration cases so often seen in actual practice: those receiving retreatment, those with clinical indication of resistance to the drugs being use, those with residual open cavities not amenable to collapse or removal, and those patients who are unwilling or unable to take uninterrupted therapy for very long periods. There is an increasing body of opinion to suggest indefinitely prolonged chemotherapy in many such cases.[82]

Use of Steroids in Patients With Known or Possible Tuberculosis.—In the early days of cortisone therapy numerous instances of breakdown of latent tuberculosis were reported.[83] After much cautious experimentation it has now been confirmed in many clinics that full dosage steroid therapy may be given with impunity, and at times benefit, to patients under cover of effective chemotherapy.[84] One should be sure to use an effective antituberculosis regimen and be as sure as possible that the patient's organisms are not resistant to the chemotherapeutic agents being used.

REST AND GENERAL MANAGEMENT

There was controversy over the place of rest in the therapy of tuberculosis long before the advent of chemotherapy in 1946; it is even more an unsettled question today. There is little doubt that rest has an important antituberculosis effect. There can be no argument about this in the light of the changes in mortality which took place following the introduction of systematic rest around the turn of the century.[1,64] There is considerable argument, however, as to the mode of its action. Early in this century emphasis was laid upon the general nonspecific effect of rest, the stimulation of the natural resistive powers of the host and general lung and body rest, with a tendency thus to localize the organisms and reduce their dissemination about the body.

As far as the lung is concerned, there is no argument with this reasoning except that it is probably incomplete. The horizontal position may partially explain the effectiveness of rest as follows. In the first place, the horizontal position causes a slight, pneumoperitoneum-type, bilateral lung collapse by a higher diaphragmatic position in all phases of breathing. Second, the horizontal position apparently increases the circulation of blood in the pulmonary vessels in the upper lungs.[85] This causes increased diffusion of gases which in turn lowers alveolar oxygen tension and thus may make these commonly involved areas less favorable to the growth and multiplication of *Myco. tuberculosis*.[86]

It has been well established that patients receiving effective primary uninterrupted multiple chemotherapy have a reduced need for rest.[87,88] It is important to stress, however, that the studies on which this statement is based concern patients who have not been at work, who have been separated from many of the stresses of ordinary life, and who have often been confined to a hospital environment for long periods. In short, horizontal bed rest is one thing, rest in a hospital or sanatorium is another, and both are quite different from being at home or at work.

VOL.
4
1956

A period of rest in a tuberculosis hospital or sanatorium for a minimum of two to six months has a very important place at the outset of treatment of any case of tuberculosis.[89] Except for the well-indoctrinated, intelligent, and mildly ill ex-patient, all will benefit materially from a period of indoctrination and education, all must learn to take their disease with appropriate seriousness and learn the necessity of accepting various kinds of treatment which may at times be considerably worse than the symptoms of their disease. The vital initial period of close and frequent observation can be most effectively accomplished in the hospital. Desensitization can be carried out in case of drug hypersensitivity. Drug dosage or administration can be altered in case of toxicity or intolerance. Especially in the retreatment case, indications of clinical resistance after therapy has been instituted can be spotted early and treated by an appropiate change in regimen.

Rest for pulmonary tuberculosis under effective chemotherapy has actually been opposed on theoretical grounds as follows: the drugs act only on actively multiplying bacilli and keeping the patient active is one way to encourage all living bacilli still present in the host to multiply actively (another is to administer steroid therapy and still another is purposely to avoid closing cavities[88]). While this is an ingenious concept, there appear to be strong arguments against it. Persistence of cavity during chemotherapy promotes drug resistance.[61] "Open healed" cavities may not be healed in fact and may be a potent source of relapse. They may also become secondarily infected. The strongest argument against this concept is that it minimizes the all-important host factors presumably promoted by rest, and places total reliance upon drugs and resectional surgery. Finally, even though one accepts this theory and acts upon it, there can be no logic whatever in withholding rest in the cases in which one cannot be sure of obtaining fully effective chemotherapeutic action.

Rest may not be necessary for certain extrapulmonary forms of the disease such as skin, lymph node, and genitourinary tuberculosis. Bone and joint

tuberculosis is clearly helped by rest, often augmented by special splints and braces. "Rest" generally is assumed to include good hygiene, a diet nutritious particularly in proteins, and all supportive measures which are thought to build the important individual immunity to the disease.

Hemoptysis is seldom fatal and if it is going to be fatal there is usually little the physician can do. Pneumoperitoneum, pneumothorax, even emergency surgical collapse or resection have all been effective in the severe but treatable cases. The patient can often tell from which side the blood is coming. The relief of fear and tension, which is accomplished most effectively by the physician's attitude, is most important. The use of morphine or its derivatives is strongly contraindicated for fear of suppressing cough too much, thus permitting blood to clot in the airways with resultant atelectasis or even suffocation.

The *psychology* of the tuberculosis patient has been an intriguing subject for many years. The best modern opinion holds that there is no characteristic tuberculosis personality and that if a psychologic defect is present it may interfere seriously with the outcome of therapy unless properly managed.[90]

The management of tuberculosis should include the protection of persons who are apt to remain in contact with the disease in any infectious state. *BCG vaccination* for the potentially heavily exposed nonreactor to tuberculin is considered standard management today.[91]

PATIENT EDUCATION

Successful treatment of chronic disease depends to a large extent upon patient cooperation. This is most effectively stimulated by increasing his knowledge of the disease, its cause, dissemination, course, and treatment. This educational procedure must be individualized according to age, personality, intelligence, and other factors, but may be planned around the following: special literature or brochures for various phases of treatment, film strips, recorded talks, group sessions with question and answer periods, and individual sessions with nurse and physician. The anticipation of objections to operation by early discussions of its possibility is most helpful in some but not in all patients. Complete frankness and honesty are good standards but at times have to be modified slightly. Education of the patient is in short painstaking, sometimes difficult, almost always time consuming, but invariably rewarding.[92]

SPECIAL THERAPY APPLICABLE ONLY TO PULMONARY TUBERCULOSIS

Collapse Therapy.—In selecting patients for collapse therapy and resection in pulmonary tuberculosis, it is necessary to consider the pulmonary functional reserve and how it may be affected by the available therapies. The history, physical examination, chest fluoroscopy, and simple clinical evaluation are all helpful. Recourse to certain tests—the maximum breathing capacity, the timed vital capacity, the lung volumes (especially residual vs. total volume), the blood gases and their response to exercise, and bronchospirometry showing the ventilation and gas exchange of each lung separately—may be invaluable in planning surgery, especially in the complicated case with considerable functional impairment.[93]

Collapse therapy is often indicated in patients with cavity. It is thought to act in the following way: reduction in lung size leads to relative or complete airlessness of the involved portions of lung which are apt to contain exudate and inflamed, weakened, and partially occluded bronchi; both of these factors encourage collapse of the involved lung; meanwhile the surrounding healthy lung continues to ventilate normally. Collapse may rarely operate in the opposite way, causing ballooning of a cavity, probably by kinking a damaged bronchus so that the cavity will admit air on inspiration and not let it out on expiration.

Collapse may be either temporary or permanent. Temporary forms of collapse include pneumoperitoneum, phrenic nerve interruption, and artificial pneumothorax.

Temporary collapse is applicable predominantly to disease which is of recent origin, with cavity walls not made unyielding by fibrosis. It is particularly applicable *early* during chemotherapy in the presence of cavity, to reduce the need for later permanent collapse or resection and to reduce the risk of drug resistance.

Pneumoperitoneum is a controversial form of temporary collapse still finding variable acceptance in the United States.[94,95,96] Unquestionably, it is less effective, but also less dangerous, than artificial pneumothorax. The location of cavity appears to influence the results of pneumoperitoneum very little except that cavity in the superior segment of a lower lobe seems to respond particularly well.[45] If it is to be used, pneumoperitoneum should be initiated either before or at the beginning of chemotherapy on the theoretical grounds that the bronchocavitary junction is more capable of complete occlusion by kinking before rather than after epithelization.[97] The initial filling varies from 300 to 500 c.c. with refills given at 3 to 14 day intervals in amounts ranging from 700 to 1,500 c.c. If pneumoperitoneum fails to produce a good diaphragmatic rise or a satisfactory reduction in the size of cavity, or is not tolerated well, it should be abandoned in from one to three months. Pneumoperitoneum is often effective as a temporary space reducer at the time of resection; it should be instituted prior to the resection rather than afterward, since rapid formation of postoperative adhesions will prevent any upward displacement of the lung once it is fixed low in the thorax. Pneumoperitoneum need be continued only for twelve to twenty-four months after disappearance of cavity and conversion of sputum, unless thoracoplasty or resection is introduced; in the latter case the refills are stopped 4 to 6 weeks after surgical intervention is complete. Rarely phrenic nerve interruption is added to pneumoperitoneum, especially in cases in which other thoracic surgery is contraindicated. The danger of pneumoperitoneum lies predominantly in air embolism, which is caused by the forcible injection of air into the liver, spleen, or abdominal wall. It can be prevented by inserting the needle below and to the left of the umbilicus, by making sure of good contact with the peritoneal space, and by avoiding the injection of air into a bleeding needle tract. Subcutaneous, mediastinal, and scrotal emphysema are occasional causes of discomfort but are not serious.

VOL.
4
1956

Artificial *pneumothorax* may have been cast aside too soon in this country, and probably still is useful where expert thoracic surgery is not available. It fell into disrepute for good reason when it became clear that the serious complications of empyema, bronchopleural fistula, fibrothorax, and unnecessary loss of pulmonary function were ultimately very frequent, prior to the concomitant use of effective chemotherapy.[98,99] Now it is reported that the risk of empyema, the major complication of pneumothorax, has been reduced almost to zero by concomitant chemotherapy. It is important to remember, however, that even though the early risks of pneumothorax may be less than those of surgery,[100] the real test of preference between the two is a long period of observation, because complications of prechemotherapy pneumothorax continued to occur for many years after refills had ceased. Initial filling is usually from 300 to 500 c.c., with refills ranging from 3 to 21 days, occasionally longer, with the amounts of refills ranging from 100 to 600 c.c. The amount of refill needed is reduced with the passage of time because of gradual thickening of the pleura and slower absorption of air. Practically all artificial pneumothoraces will benefit from routine thoracoscopy in search of adhesions, especially adhesions over cavitary areas, and most will be improved by adhesion cutting. The result of a pneumothorax is usually as good as its freedom from adhesions.

Phrenic nerve interruption was originally accomplished by means of avulsion or section of the nerve; later the nerve was crushed to avoid permanent paralysis. In recent years the procedure has been virtually abandoned in this country because of its relative ineffectiveness and the risk, even with crushing, of permanent loss of pulmonary function.[101] It may still be effective to supplement a rare pneumoperitoneum in a patient not suitable for other collapse or resection.

Permanent collapse may be achieved either by thoracoplasty or plombage.

Thoracoplasty is actually the surgical shortening of from five to ten ribs; it is accomplished by subperiosteal resection of varying lengths of rib, from the entire first rib to a short segment of the lowest rib removed. The portions of rib removed are predominantly posterolateral because most disease is located posteriorly and because removal of long lengths of two or more anterior ribs is potentially quite damaging to pulmonary function.[93] The operation is accomplished in two or three operative stages; this is in order to prevent mediastinal flutter, atelectasis, and cardiopulmonary failure from a large decostalized area of chest wall. The operations are spaced at from 2 to 5 weeks, preferably 2 to 3, in order to avoid loss of collapse from bony regeneration before completion of the collapse. Solid new ribs regenerate from the periosteum unless this is discouraged or delayed by the application of formalin or a pack. Collapse is achieved predominantly, it is believed, by relaxation of underlying lung rather than by positive pressure. The chief indication for thoracoplasty is persistence of cavity during therapy, preferably in the upper posterior area. If the cavity is anterior or in the mid or lower lung fields, the chances of effective collapse by thoracoplasty are limited. It is also used to reduce the size of the hemithorax in tuberculous empyema, both primary and secondary to pneumothorax, and for the space problems following resection with or without bronchopleural fistula.

VOL 4 195

The spinal deformity of thoracoplasty can be minimized by limiting the resection of transverse processes and muscular attachments and by persistent and thorough physiotherapy. Bilateral thoracoplasty is occasionally used, but from a pulmonary functional standpoint is inadvisable except in young individuals with very good function. Even in favorable cases it is advisable to confine the collapse to a total of no more than eleven ribs on the two sides. Thoracoplasty was repeatedly shown to be our most effective form of treatment for pulmonary tuberculosis, as measured by long-term observation, prior to the advent of modern chemotherapy.[102] It is still very useful, particularly in the chronic, extensive, drug-resistant case in which the risks with resection are much less attractive.

One can also accomplish a thoracoplasty type of collapse by the use of *plombage*. The material used in the plomb has varied over the years; currently the most popular material is methyl methacrylate (Lucite) spheres sealed in a polyethylene bag, or folded polyethylene sheets. The plomb is placed between the lung and periosteum centrally and the deperiostealized ribs peripherally. The plomb and denuded ribs in these cases are removed after three to five months, by which time the new chest wall is sufficiently stabilized to continue to prevent mediastinal flutter. An alternative method applicable to the patient past 60 years of age is the permanent plombage. In this operation a portion of the periosteum is retained on the outer surface of each rib in order to preserve some of its blood supply; the patient thus ends up with two sets of ribs separated by the plomb. The extent of deperiostealization and the size of the plomb in each method are determined by the location and size of the cavity to be collapsed. A plombage should not be used in the presence of empyema or chronic chest wall infection. In plombage the collapse is accomplished by pressure as well as by relaxation. The fact that the first rib is left in reduces the spinal deformity to a minimum. Results have been evaluated now for four or five years, and are quite encouraging, with a very low incidence (1-4 per cent) of wound infection. Complications apparently can be minimized by restricting periosteal dissection on the spinal rib ends so as to avoid entry of the plombage into the mediastinum.[103] These operations must not be confused with the very hazardous early types of intrapleural Lucite plombage long since discredited.

Resection.—The surgical removal of tuberculous lung tissue has been performed sporadically for many years, but its widespread successful use has accompanied the advent of effective chemotherapy. It has been stressed that disease confined to a segment or two may be resected safely without chemotherapy if painstaking dissection along natural anatomic planes and sound pre- and postoperative care are practiced.[104] Patients under effective chemotherapy, on the other hand, can tolerate less meticulous removal of much less favorable disease.

It is another story when such operations are performed in the presence of bacterial resistance to the drugs being employed. Complications, particularly air leaks, bronchopleural fistula, and empyema are about as frequent as they were before the introduction of effective chemotherapy,[105] with the exception that INH seems to exert some protection in many patients who excrete INH-resistant bacilli.

The complications of resection may also be reduced by skillful postoperative care, such as by encouraging the patient to breathe deeply and to cough, by judicious bronchoscopy and tracheostomy, and with physiotherapy.

Pulmonary resections range from total unilateral pneumonectomy and lobectomy to segmental lobectomy and subsegmental or wedge resections, plus combinations of these types. There is an increasing tendency to perform resections along segmental planes as nearly as possible.

The principal controversies in this field today concern indications, timing, and the need for "covering" thoracoplasty. There is little disagreement over the standard indications—destroyed lung, localized symptomatic bronchiectasis, major bronchial obstruction, and the "open positive" cavitary infectious lesion which persists during prolonged chemotherapy.[106] There is increasing doubt of the need for removing the "closed negative" lesions, although some feel that those which were formerly cavitary or are greater than 2 cm. in diameter are better out than in. Observations three years after the completion of twelve months or more of original chemotherapy show no difference in the low relapse rate (about 7 per cent) between resection and no resection for "closed negative" lesions of all types.[107,108]

There appears to be no hard and fast rule to be laid down with regard to indications for resection; rather, there are various considerations which militate for and against the procedure. These are outlined—not necessarily in the order of their importance—in Table IV. The chance of achieving cavity closure

TABLE IV. FACTORS INFLUENCING THE DECISION TO RESECT TUBERCULOUS LUNG

FACTOR	FOR RESECTION	AGAINST RESECTION
Cavity	Persists during chemotherapy	Closes promptly or never present
Cavity closure	By "filling in"	By gradual shrinkage
Basic chemotherapy	Retreatment or poorly or questionably "effective"*	Original and "effective"*
Location of cavity	Superior segment, mid-lung, or base, i.e., unsuitable for thoracoplasty type of collapse	Not pertinent
Sputum bacteriology	Failure or delay in conversion	Prompt and persistent conversion
Reliable drug coverage for operation	Available	Not available or questionable
Bronchoscopically visible bronchi	No active tuberculous process	Inflammatory tuberculosis
Pulmonary function	Satisfactory	Marginal or poor
General condition	Satisfactory	Unsatisfactory

*By "effective" chemotherapy is meant a well-established combination of two or more drugs given in adequate dosage essentially without interruption to an individual whose organisms have been shown or can be presumed to be susceptible to the agents being used.

VOL 4 195

diminishes as time on chemotherapy passes.[108] It is generally agreed that the law of diminishing returns in cavity closure takes over after about six months on primary chemotherapy; it may be even earlier on retreatment chemotherapy.

The use of thoracoplasty to cover resection is often recommended to correct or reduce the hazard of air leaks and pleural infection. There is little support today for the theory that preventing or reducing overdistention will protect lung function or prevent breakdown of residual tuberculous foci. The need for covering thoracoplasty can be determined best by observing whether the remaining lung will expand to fill the space, both at the time of operation and during the ensuing 2 to 12 weeks. Covering thoracoplasty is best not performed at the same time as resection because of the added operative trauma and risk. If thoracoplasty precedes resection it may turn out not to have been necessary; there is good reason in dangerous cases, however, to try conventional thoracoplasty first and to resect later if necessary. If thoracoplasty follows the resection it may be of the "tailoring" variety, in particular, leaving in the first rib and thus adding much to good posture and comfort. The need for space-filling thoracoplasty may be reduced by using pneumoperitoneum before, during, and for several weeks after a major resection.

OL.
4
956

As far as timing is concerned, it now appears that resection can be performed both safely and effectively early in the course of chemotherapy, provided all the visible and palpable disease is removed. Two objections to early resection are: (1) the amount of lung tissue removed may be significantly reduced by waiting, and (2) resection may not even be necessary. There is much to suggest that the roentgenographic clearing commonly noted during the early months of chemotherapy often represents simply shrinkage of diseased lung with overexpansion of adjacent good lung. Thus by waiting six to twelve rather than one or two months to resect, the surgeon may remove a smaller-looking specimen, but one which is simply the shrunken remnant of what he would have removed earlier. This reasoning applies only to a select group of patients, usually those with cavitary disease in no more than one or two segments, but ones who might well be saved many months of hospitalization by early surgical intervention.

There is increasing interest in cavernectomy, i.e., the removal of cavities from within diseased lung in patients with too extensive disease to permit removal of all or most of it.[109] These are mostly the poor-risk patients with manifest drug resistance who appear to me to be much better candidates for thoracoplasty or plombage thoracoplasty than for resection, unless the cavity is poorly located for surgical collapse.

Other Thoracic Surgical Procedures.—Cavernostomy has become less hazardous and hence potentially a very effective weapon in association with chemotherapy, especially for the huge, peripheral, blocked cavity.[110] Closed cavity (Monaldi) drainage still has a small but important place.[111] Decortication is useful in well-selected cases to re-expand lungs bound down by a heavy peel following pleurisy.[112]

SPECIAL COMMENTS REGARDING THE THERAPY OF EXTRAPULMONARY TUBERCULOSIS

All forms of extrapulmonary tuberculosis respond quite well to specific antituberculosis chemotherapy. This is particularly true of the larynx, bronchus,

ear, mucous membrane, tendon sheath, bursa, and skin. Uncomplicated miliary tuberculosis also responds promptly and well to chemotherapy. While the inflammatory reaction of a tuberculous pericarditis may be controlled by chemotherapy, this may not prevent the later onset of constrictive pericarditis.[113] Simple tuberculous pleurisy with effusion should be regarded and treated as advanced pulmonary tuberculosis; it usually responds well to chemotherapy plus aspiration for dyspnea or mediastinal shift. Decortication of residual pleural "thickening" in these cases should be considered but usually only after six to twelve months of therapy because of the possibility of delayed spontaneous clearing. Tuberculous empyema, especially when the infection is mixed, often requires surgical drainage and sometimes permanent surgical reduction in size of the thorax in addition.

Endobronchial tuberculosis was a very serious complication of pulmonary tuberculosis before chemotherapy had a major influence on its outcome; this was true especially when pneumothorax or resection was used in its presence.[98] Chemotherapy has proved sufficiently effective that routine presurgical bronchoscopy has been abandoned in some clinics. It is probably best, however, to look and be sure of the appearance of any bronchus that is to be transected.[114]

Accumulations of tuberculous pus in any part of the body often require surgical drainage despite specific and highly effective chemotherapy. A good example of this is bone tuberculosis, especially with associated osteomyelitis; drainage and removal of bone sequestra are still indicated. Once there is any evidence of destruction of the bone or cartilage in an actively moving joint, active orthopedic intervention is still recommended despite the ability to control the infection with chemotherapy.[115]

It is also current thinking that gynecologic tuberculosis frequently requires surgical intervention.[116] This point of view, in my opinion, is likely to become more conservative as time goes on. Despite adequate treatment, tuberculosis of the female genital organs is still a frequent cause of sterility.

Genitourinary tuberculosis has proved highly responsive to modern chemotherapy, especially with all three major drugs. This has actually reached the point where removal of known tuberculous lesions under such therapy has been drastically curtailed.[117]

Tuberculous meningitis, once always fatal, still carries a 10 to 15 per cent mortality, especially when associated with miliary tuberculosis. Some who recover are left with permanent brain or nerve damage. The reasons for these failures are two: first, prolonged delay in treatment because of failure to recognize the cause of the meningitis, and, second, subarachnoid block. The latter seems to respond to the administration of steroid therapy. If steroids are used, cortisone in full doses is recommended four times daily for 7 to 10 days, with gradually decreasing dosage for another 2 weeks. Patients with tuberculous meningitis should receive INH, SM, and PAS, all daily in maximum tolerated doses; this includes 2 Gm. of SM a day (in the adult) for 1 to 2 weeks and 1 Gm. a day for 4 to 6 months, after which SM may be reduced to two or three times a week.

There is disagreement on the importance of removing tuberculous lymph nodes in patients who are receiving effective chemotherapy.[118] They probably should be removed when they tend to suppurate and where the chemotherapy can be presumed to be less than fully effective—as with single-drug therapy, interruptions, inadequate duration, and very low dosage.

The frequency and severity of intestinal tuberculosis have become notably less in the past 30 years.[119] The reason for this is not known. The vast majority of intestinal lesions begin in the cecum or terminal ileum and extend upward and downward therefrom; on the other hand, tuberculous ulcerations of the stomach and upper intestinal tract without an associated iliocecal lesion have been described.[120] Intestinal tuberculosis responds well to chemotherapy; obstruction rarely necessitates intubation or surgical correction. Surgical intervention without effective chemotherapy is quite hazardous.

VOL.
4
1956

REHABILITATION

Any discussion of the management of tuberculosis would be incomplete without reference to the subject of rehabilitation. While many persons who formerly would have required rehabilitation no longer do so, there are many others who formerly would have died who now recover from tuberculosis or become "good chronics," only to live on with limited breathing reserve and hence who often need rehabilitation of the most comprehensive sort. Needless to say, a good rehabilitation program should start soon after therapy is begun in order to attain maximum benefit.

ASSOCIATION OF TUBERCULOSIS WITH OTHER MAJOR DISEASES

Diabetes Mellitus.—Uncontrolled diabetes has a seriously adverse effect on tuberculous infection and vice versa. The behavior of tuberculosis in the well-controlled diabetic patient, on the other hand, does not differ materially from its behavior in other patients.[121] Except in patients who are overweight, the diet prescribed should contain enough carbohydrate, protein (at least 75 Gm./day) and fat to satisfy the individual's hunger. Because of the importance of nutrition in tuberculosis, the diet should be altered as indicated by the patient's appetite at frequent intervals, and sufficient insulin given to cover this purposely liberal diet. It is probably best to initiate control with regular insulin, because of the prompt reduction in insulin requirement often noted as the tuberculous inflammation subsides. By the same token, simple control of diabetes occasionally used to cause a dramatic improvement in the tuberculosis before the days of chemotherapy and may, of course, still do so today. After control has been achieved with regular insulin, the change to long-acting insulins can be appropriately made. Strict control of blood sugar concentrations is urged, using both fasting and postprandial blood samples as well as the urine examinations for sugar.

Silicosis.—The silicotic lung is a fertile soil for *Myco. tuberculosis.* In spite of this, it is notoriously difficult to prove bacteriologically the coexistence of tuberculosis and silicosis. Conglomerate silicosis is thought almost always

to be complicated by tuberculosis.[122] These cases should be treated like any case of pulmonary tuberculosis except that chemotherapy should be given for very long periods because the prognosis is so apt to be poor. Only rarely will temporary collapse procedures produce any detectable collapse or benefit. More collapse may be obtained from thoracoplasty or plombage than from temporary measures but results are not too encouraging. Resection has been accomplished safely and with benefit in a few cases but at very great risk. All landmarks of segmental anatomy are so obliterated that the performance of the operation becomes a surgical nightmare. After an ill-defined piece of lung is removed in the hope that it contains the lesion being attacked, the adjoining lung cannot expand to fill the space. Prevention of silicotuberculosis is the only really dependable form of management.

Diffuse Obstructive Pulmonary Emphysema.—Focal areas of emphysema complicate healing or fibrosing pulmonary tuberculosis but present a clinical problem only when very extensive. Diffuse generalized obstructive emphysema is apparently totally unrelated to pulmonary tuberculosis but has a very adverse effect on its course. The emphysematous lung responds poorly if at all to both temporary and permanent collapse; resections performed upon these lungs are commonly complicated by air leaks, empyema, and further loss of function.[123] Until more is known of the etiology and pathogenesis of emphysema it will continue to be difficult to do much for these unfortunate individuals. Like silicosis, when all is known about emphysema, prevention, not treatment, will probably be the answer. Thorough symptomatic therapy of the emphysema and thorough rest and chemotherapy for the tuberculosis in the hope of avoiding the necessity of collapse or resection are wise. On the other hand, one should not overlook the fact that prolonged rest may cause further loss of ventilatory function in these patients; this untoward event is due to loss of the tone and strength of respiratory muscles from the reduced demand upon them during rest. Rest for the emphysematous tuberculous patient should therefore never be strict, but rather mixed with limited but regular exercise of the breathing muscles.

Pregnancy.—It is now fair to state that pregnancy is not a serious event in the course of active tuberculosis under effective chemotherapy.[124] The pregnancy is treated as if the tuberculosis were not present. In fact, the indications for therapeutic abortion in tuberculosis have practically disappeared except in the seriously ill patient with very far-advanced, drug-resistant disease. Sterilization to prevent increasing the burden of certain tuberculous mothers is a sound consideration.

THE RESULTS OF PRESENT-DAY TREATMENT

In considering the results of present-day treatment one should first consider results in the very select patients who are cooperative, who remain under adequate management until maximal hospital benefit has been achieved, and who pursue postdischarge treatment and observation in a satisfactory manner. This question can be answered at this time only as an average of experiences and opinion on three to five years' observation.[1,3,54,102,107,108,125-129]

When such an ideal patient has minimal pulmonary tuberculosis at the outset, the regression rate is virtually 100 per cent, the relapse rate is about 5 per cent, and the mortality rate approximately zero.

With moderately advanced lesions, 90 to 95 per cent are estimated to regress to inactivity, the three- to five-year relapse rate is around 5 to 7 per cent, and the mortality rate in this short period can be no more than 1 to 2 per cent.

Far-advanced pulmonary tuberculosis in these favorable patients has regressed to inactivity in 80 to 85 per cent; relapse of these has occurred in 7 to 10 per cent and mortality from tuberculosis has occurred in 5 to 10 per cent.

In short, our most effective modern treatment is by no means perfect, even when selected and administered as expertly, and accepted as wholeheartedly, as possible. Another phenomenon in this new tuberculosis mortality picture is that the majority of deaths in this select group are not the result of progressive tuberculosis, but rather of the late effects of destroyed lung tissue and some surgical complications.

VOL.
4
1956

The trouble with these estimates is that in practice many patients either fail to take good advice or receive poor therapy or both. A significant proportion of these people are constitutionally inadequate, psychopathic personalities, mental defectives, and/or alcoholics. Results in these cases are much poorer than in the favorable group but are admittedly not as poor as one might anticipate them to be. In short, while many of these patients remain invalids and chronically infectious, death from progressive tuberculosis is still less common than death from respiratory insufficiency and chronic cor pulmonale.

Before closing this discussion, attention should be given to some of the special social problems which face us today. The disease is found predominantly in males, most of whom are past 40 and often much older, and usually without a family or a decent home. *Social services* for these patients in particular are both extremely important and often virtually impossible to apply. Alcoholism in these tuberculous patients is an almost insoluble problem. How can we persuade an alcoholic to take prolonged and often difficult treatment for tuberculosis when by virtue of his alcoholism he has repeatedly demonstrated complete lack of interest in his health and future? Social services for other less derelict tuberculous individuals continue to play an important and even growing role in the over-all management of the disease.

Accompanying the excessive optimism which followed the advent of effective chemotherapy, there has been a gradual diminution in respect for the communicability of the disease. Some states and communities, on the other hand, have taken legal steps to protect themselves from the recalcitrant infectious tuberculous patient; many still remain officially indifferent to this real menace. Have we not come to the point where we should repeatedly and emphatically seek out the remaining foci of infection in our own communities and restrain if necessary those infectious individuals who repeatedly and brazenly refuse to segregate themselves voluntarily from their fellow men?

SUMMARY

1. The present-day management of tuberculosis is reviewed, with special emphasis on pulmonary tuberculosis.

2. The treatment of tuberculosis includes rest, education, chemotherapy, surgical drainage and extirpation, and rehabilitation. The therapy of pulmonary tuberculosis also includes lung collapse and certain specialized surgical procedures.

3. Considerations of chemotherapy include concepts of mode of action, indications, regimens, dosage, duration, in vitro and in vivo drug susceptibility, toxicity, interruptions, early ambulation, original therapy vs. retreatment, new agents, and results to date.

4. Special emphasis is paid to INH metabolism, individual variations in the speed and degree of INH inactivation, dosage, and the effects on INH blood levels of the concurrent administration of PAS.

5. Other features of management are discussed, including the increasing difficulties in differentiating tuberculosis from other diseases with certainty, the increasing social problem of the tuberculous alcoholic, and the place of enforced hospitalization of the recalcitrant infectious tuberculous patient.

6. Results of modern treatment are presented and discussed.

I wish to express appreciation to Drs. Gardner Middlebrook, Curtis Carter, Gordon Meiklejohn, William B. Tucker, and J. Carroll Bell for helpful suggestions in the preparation of this manuscript.

VOL 4 195

REFERENCES

1. Anderson, R. J.: Tuberculosis Morbidity and Mortality Facts and Trends, Pub. Health Rep. **71**:194, 1956.
2. Drolet, G. J.: Present Trend of Case Fatality Ratios in Tuberculosis, Am. Rev. Tuberc. **37**:125, 1938.
3. Drolet, G. J., and Lowell, A. M.: Whereto Tuberculosis? The First Seven Years of the Antimicrobial Era. Am. Rev. Tuberc. **72**:419, 1955.
4. Long, E.: Unpublished data.
5. Buhler, V. B., and Pollak, A.: Human Infection With Atypical Acid-Fast Organisms, Am. J. Clin. Path. **23**:363, 1953.
6. Timpe, A., and Runyon, E. H.: The Relationship of Atypical Acid-Fast Bacteria to Human Disease. A Preliminary Report, J. Lab. & Clin. Med. **44**:202, 1954.
7. Hinshaw, H. C., and Garland, L. H.: Diseases of the Chest, Phila. 1956, W. B. Saunders.
8. Weed, L. A., Anderson, H. A., Good, C. A., and Bagenstoss, A. H.: Nocardiosis, Clinical Bacteriologic and Pathological Aspects, New England J. Med. **253**:1137, 1955.
9. Furculow, M. L.: Further Observations on Histoplasmosis; Mycology and Bacteriology, Pub. Health Rep. **65**:965, 1950.
10. Baum, G. L. and Schwartz, J.: Coccidioidomycosis—A Review, Am. J. Med. Sc. **230**:82, 1955.
11. Furculow, M. L., and Brasher, C. A.: Chronic Progressive (Cavitary) Histoplasmosis as a Problem in Tuberculosis Sanatoriums, Am. Rev. Tuberc. **73**:609, 1956.
12. Davis, E. W., Katz, S., and Peabody, J. W., Jr.: Calcification Within the Solitary Pulmonary Nodule, Am. Rev. Tuberc. **74**:106, 1956.
13. Palmer, C. E.: Tuberculin Sensitivity and Contact With Tuberculosis, Am. Rev. Tuberc. **68**:678, 1953.
14. Connar, R. G.: Prescalene and Deep Cervical Lymph Node Biopsy, Surg., Gynec. and Obst. **191**:733, 1955.
15. Jones, J. S.: Intravenous PAS in Relation to Pulmonary Tuberculotherapy, Brit. J. Tuberc. **48**:286, 1954.
16. Tucker, W. B., Jr.: Comparative Efficacy of Three Streptomycin and PAS Regimens of Prolonged Duration in Patients With Previously Untreated Pulmonary Tuberculosis, Am. Rev. Tuberc. **72**:733, 1955.
17. Medical Research Council (British): Various Combinations of Isoniazid With Streptomycin or With Para Aminosalicylic Acid in the Treatment of Pulmonary Tuberculosis, Brit. M. J. **1**:435, 1955.
18. United States Public Health Service: Co-operative Clinical Investigation of Chemotherapy Regimens for Tuberculosis. Unpublished data.
19. Morse, W. C.: Unpublished data.
20. Hughes, H. B.: On the Metabolic Fate of Isoniazid, J. Pharmacol. & Exper. Therap. **109**:444, 1953.

21. Cuthbertson, W. F. J., Ireland, D. M., and Wolff, W.: Detection and Identification of Some Metabolities of Isonicotinic Acid Hydrazide (Isoniazid) in Human Urine, Biochem. J. **55**:669, 1953.
22. Hughes, H. B., Schmidt, L. H., and Biehl, J. P.: The Metabolism of Isoniazid: Its Implications for Therapeutic Use of the Drug, Tr. 14th Veterans Administration-Armed Forces Conf. on Chemotherapy of Tuberculosis, Atlanta, Feb., 1955.
23. Biehl, J. P.: Role of the Dose and Metabolic Fate of Isoniazid in the Emergence of Isoniazid Resistance, Tr. 15th Veterans Administration-Armed Forces Conf. on Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
24. Barclay, W., Ebert, R. H., and Koch-Weser, D.: Mode of Action of Isoniazid, Am. Rev. Tuberc. **67**:490, 1953, and **70**:784, 1954.
25. Johnson, W. J.: Biological Acetylation of Isoniazid, Nature, **174**:744, 1954.
26. Morse, W. C., Curry, F. J., Morse, P. Z., Chambers, J. S., and Lincoln, A. F.: Effect of Oral PAS on Biologically Active Isoniazid Serum Levels, Tr. 15th Veterans Administration-Armed Forces Conf. on Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
27. Mandel, W., Cohn, M. L., Russell, W. F., Jr., and Middlebrook G.: Effect of PAS on Serum Isoniazid Levels in Man, Proc. Soc. Exper. Biol. & Med. **91**:409, 1956.
28. Bell, J. C., Riemensnider, D. K., and Mitchell, R. S.: The Effect of Certain Aromatic Amines on Serum Levels of Biologically Active Isoniazid in Humans. Unpublished data.
29. Russell, W. F., Jr., and Middlebrook, G.: Persistent Excretion of Isoniazid-susceptible Tubercle Bacilli, Tr. 15th Veterans Administration-Armed Forces Conf. on Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
30. Tucker, W. B., Jr.: Randomized Basic Regimes (Isoniazid-PAS, Isoniazid-Streptomycin, Streptomycin-PAS): Clinical Discussion, Tr. 15th Veterans Administration-Armed Forces Conf. on Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
31. Therapeutic Trials Committee, Swedish National Ass'n. against Tuberculosis: Isoniazid, PAS and Streptomycin in Pulmonary Tuberculosis, Acta tuberc. scandinav. **30**:165, 1955.
32. Way, E. L., Peng, C. T., Allawala, N., and Daniels, T. C.: The Metabolism of PAS in Man, J. Am. Pharm. A. **44**:65, 1955.
33. Elmendorf, D. F., Jr., Cawthon, W. U., Muschenheim, C., and McDermott, W.: The Absorption, Distribution, Excretion and Short Term Toxicity of Isoniazid (Nydrazid) in Man, Am. Rev. Tuberc. **65**:429, 1952.
34. Mackaness, G. B., and Smith, N.: The Bactericidal Action of Isoniazid, Streptomycin and Terramycin on Extracellular and Intracellular Tubercle Bacilli, Am. Rev. Tuberc. **67**:322, 1953.
35. Schaefer, W. B.: The Effect of Isoniazid on Growing and Resting Tubercle Bacilli, Am. Rev. Tuberc. **69**:125, 1954.
36. Mitchison, D. A.: Problems of Drug Resistance, Brit. M. Bull. **10**:115, 1954.
37. D'Esopo, N.: Prolonged Chemotherapy of Pulmonary Tuberculosis, Tr. 8th Veterans Administration-Armed Forces Streptomycin Conf., Atlanta, Nov., 1949.
38. Mahady, S. C. F., Armstrong, F. L., Beck, F., Horton, R., and Lincoln, N. S.: A Comparative Study of Streptomycin and Dihydrostreptomycin in Pulmonary Tuberculosis, Am. Rev. Tuberc. **68**:238, 1953.
39. Hobson, L. B., Lynch, W., and Hinshaw, H. C.: Further Experience With a Mixture of Streptomycin and Dihydrostreptomycin in Pulmonary Tuberculosis, Tr. 13th Veterans Administration-Armed Forces Conf. on Chemotherapy of Tuberculosis, St. Louis, Feb., 1954.
40. Biehl, J. P., and Vilter, R. W.: Effect of Isoniazid on Vitamin B_6 Metabolism; Its Possible Significance in Producing Peripheral Neuritis, Proc. Soc. Exper. Biol. & Med. **85**:389, 1954.
41. Selikoff, I. J., Robitzek, E. H., and Ornstein, G. G.: Treatment of Pulmonary Tuberculosis With Hydrazine Derivatives of Isoniazid, J.A.M.A. **150**:976, 1952.
42. Benson, W. M., Stefko, P. L., and Roe, M. D.: Pharmacologic and Toxicologic Observations on Hydrazide Derivatives of Isoniazid (Rimifon, Marsilid), Am. Rev. Tuberc. **65**:376, 1952.
43. Mitchell, R. S.: Fatal Toxic Encephalitis Occurring During Iproniazid Therapy in Pulmonary Tuberculosis, Ann. Int. Med. **42**:417, 1955.
44. Mitchell, R. S., Schmidt, J., Capel, L. H. and Scheel, L.: Study of PAS Intolerance in Tuberculosis of Lung, J.A.M.A. **156**:124, 1954.
45. Mitchell, R. S.: Unpublished data.
46. Brinkman, G. L., and Coates, E. O., Jr.: The Goitrogenic Effect of PAS During the Therapy of Pulmonary Tuberculosis, Am. Rev. Tuberc. **69**:458, 1954.
47. Bellamy, W. E., Manck, H. P. J., Hennigar, G. R., and Wigod, M.: Jaundice Associated With the Administration of Sodium PAS: a Review of the Literature and Report of a Case, Ann. Int. Med. **44**:764, 1956.

OL.
4
956

48. Yegian, D., and Vanderlinde, R. J.: The Resistance of Tubercle Bacilli to Chemotherapeutic Agents, Am. Rev. Tuberc. **61**:483, 1950.
49. Demerc, M.: Genetic Basis of Acquired Drug Resistance, Pub. Health Rep. **70**:817, 1955.
50. U. S. Veterans Administration-Armed Forces Cooperative Controlled Studies of Chemotherapy for Tuberculosis.
51. Rist, N.: Transactions of Symposium on Tuberculosis in Infancy and Children, Nat. Jewish Hosp., Denver, Colo., 1955.
52. Russell, W. F., Jr., Dressler, S. H., and Middlebrook, G.: Chemotherapy of Tuberculosis. Advances in Internal Medicine, Chicago, 1956, The Year Book Publishers, Inc., vol. 8.
53. Canetti, G.: Some Inaccuracies in the Currently Employed Methods of the Determination of Isoniazid Resistance of Tubercle Bacilli—Their Extent and Consequences, Bull. Internat. Union Against Tuberculosis, **25**:149, 1955.
54. Mitchell, R. S.: Early Results of Prolonged Streptomycin-PAS Treatment of Pulmonary Tuberculosis, Ann. Int. Med. **41**:282, 1954.
55. Coates, E. O., Jr., Meade, G. M., Steenken, W., Jr., Wolinsky, E., and Brinkman, G. L.: The Clinical Significance of the Emergence of Drug Resistant Organisms During the Therapy of Pulmonary Tuberculosis With Hydrazides of Isoniazid, New England J. Med. **248**:1081, 1953.
56. Fox, W., and Sutherland, I.: The Clinical Significance of Positive Cultures and of Isoniazid-Resistant Tubercle Bacilli During the Therapy of Pulmonary Tuberculosis, Thorax, **10**:85, 1955.
57. Ostreicher, R., Dressler, S. H., Russell, W. F., Jr., Grow, J. B., and Middlebrook, G.: Observations on the Pathogenicity of Isoniazid-Resistant Mutants of Tubercle Bacilli From Tuberculous Patients, Am. Rev. Tuberc. **71**:390, 1955.
58. Middlebrook, G., Cohn, M. L., and Schaefer, W. B.: Studies on Isoniazid and Tubercle Bacilli, III. The Isolation, Drug-Susceptibility and Catalase-Testing of Tubercle Bacilli From Isoniazid Treated Patients, Am. Rev. Tuberc. **70**:852, 1954.
59. Russell, W. F., Jr., and Middlebrook, G.: Persistent Excretion of Isoniazid Susceptible Tubercle Bacilli, Tr. 15th Veterans Administration-Armed Forces Conf. on Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
60. Schmidt, L. H. Unpublished data.
61. Mitchell, R. S.: The Relation of Cavity to the Development of Streptomycin Resistant Tubercle Bacilli in Pulmonary Tuberculosis, New England J. Med. **241**:450, 1949.
62. Bignall, J. R., Clegg, J. W., Crofton, J. W., Smith, B. T. D., Holt, H. D., Mitchison, D. A., and Armitage, P.: Intermittent Dosage in the Therapy of Pulmonary Tuberculosis With Streptomycin. Brit. M. J. **1**:1224, 1950.
63. Dye, W. E., Tucker, W. B., Jr., Livings, D. B., and Williams, J. H., Jr.: The Emergence of Bacterial Resistance During the Chemotherapy of Pulmonary Tuberculosis, Am. Rev. Tuberc. To be published.
64. Dubos, R., and Dubos, J.: The White Plague. Tuberculosis, Man and Society, Boston, 1952, Little, Brown and Company.
65. Cummings, M. M.: Results of the Streptomycin "Screening Test," Tr. 12th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, Atlanta, Feb., 1953.
66. Chaves, A. D., Robins, A. B., Abeles, H., Peizer, L. R., Dangler, D., and Widelock, D.: The Prevalence of Streptomycin and Isoniazid-Resistant Strains of M. Tuberculosis in Patients With Newly Discovered and Untreated Active Pulmonary Tuberculosis, Am. Rev. Tuberc. **72**:143, 1955.
67. Steenken, W., Jr.: Streptomycin and the Tubercle Bacillus, *in* Riggins, H. M., and Hinshaw, H. C., editors: Section III, Streptomycin and Dihydrostreptomycin in Tuberculosis, 1949, Nat. Tuberculosis Assn.
68. Tucker, W. B., Jr.: Retreatment of Advanced Pulmonary Tuberculosis With Viomycin, Am. Rev. Tuberc. **70**:812, 1954.
69. Schwartz, W. S., and Moyer, R. E.: The Chemotherapy of Pulmonary Tuberculosis With Pyrizinamide Used Alone and in Combination With Streptomycin, PAS or Isoniazid, Am. Rev. Tuberc. **70**:413, 1954.
70. McCune, R. M., Jr., Tompsett, R., Muschenheim, C., Organick, A., Batten, J., and McDermott, W.: Pyrizinamide-Isoniazid in Animals and Man, Tr. 14th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, Atlanta, 1955.
71. Phillips, S., and Horton, G. E.: Pyrizinamide-Isoniazid, Am. Rev. Tuberc **73**:704, 1956.
72. Perry, C. R., and Morse, W. C.: The Pyrizinamide Susceptibility of Isoniazid-Resistant Mutants of Tubercle Bacilli, Am. Rev. Tuberc. **72**:840, 1955.
73. Livings, D. G.: Pyrizinamide-Isoniazid: Summarized Data From Randomized Study, Tr. 15th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
74. McDermott, W., Ormond, W., Muschenheim, C., Deutschle, K., McCune, R. M., Jr., and Tompsett, R.: Pyrizinamide-Isoniazid in Tuberculosis, Am. Rev. Tuberc. **69**:319, 1954.

VOL 4 195

75. Miller, F. L., Sands, J. H., Walker, R., Dye, W. E., and Tempel, C. W.: Combined Therapy With Streptomycin-Terramycin, a Pilot Study, Tr. 11th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, 1952.
76. Stewart, S. M., Turnbull, F. W. A., and Crofton, J. W.: The Use of Oxytetracycline in Preventing or Delaying Isoniazid Resistance in Pulmonary Tuberculosis, Brit. M. J. **2**:1508, 1954.
77. Schmidt, L. H.: Cycloserine in Tuberculosis of the Rhesus Monkey, Tr. 15th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
78. Epstein, L. G., and Nair, K. G. S.: Treatment of Human Tuberculosis With Cycloserine. A Progress Report, Dis. Chest **29**:241, 1956.
79. Livings, D. G.: Current Data From Cooperative Study on Cycloserine, Tr. 15th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
80. Muschenheim, C.: A Schema of Chemotherapy in Tuberculosis, Am. Rev. Tuberc. **72**:1 1955.
81. United States Public Health Service: Cooperative Clinical Investigation of Chemotherapeutic Prophylaxis of Tuberculous Maningitis in Children, Proc. Internat. Pediatric Congress, Copenhagen, July, 1956. To be published.
82. Dooneief, A. S., and Hite, K. E.: Indefinitely Prolonged Chemotherapy for Tuberculosis, Am. Rev. Tuberc. **72**:219, 1954.
83. Committee on Therapy, American Trudeau Society: The Effect of Cortisone and/or Corticotropin on Tuberculous Infection in Man, Am. Rev. Tuberc. **66**:254, 1952.
84. Johnson, T. R., and Davey, W. N.: Cortisone, Corticotropin and Antimicrobial Therapy in Tuberculosis in Animals and Man, Am. Rev. Tuberc. **70**:623, 1954.
85. Martin, C. J., Cline, F., Jr., and Marshall, H.: Lobar Alveolar Gas Concentrations: Effect of Body Position, J. Clin. Invest. **32**:617, 1953.
86. Dock, W.: Effect of Posture on Alveolar Gas Tension in Tuberculosis, Explanation of Favored Sites of Chronic Pulmonary Lesions, Arch. Int. Med. **94**:700, 1954.
87. Wier, J. A.: In-Patient Ambulatory Therapy of Tuberculosis. Preliminary Report, Tr. 15th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
88. Dressler, S. H., Anthony, E. W., Russell, W. F., Jr., Grow, J. B., Denst, J., Cohn, M. L., and Middlebrook, G.: Ambulation of Patients With Pulmonary Tuberculosis Under Protection of Chemotherapy, Am. Rev. Tuberc. **70**:1030, 1954.
89. Mitchell, R. S.: Sanatorium Treatment for Tuberculosis, J.A.M.A. **154**:1024, 1954. Correspondence.
90. Wittkower, E.: A Psychiatrist Looks at Tuberculosis, London, 1955, National Assn. for the Prevention of Tuberculosis.
91. Long, E. R.: B. C G Vaccination, Ann. Int. Med. **41**:647, 1954. Editorial.
92. Mitchell, R. S.: Teaching the Patient About His Chronic Pulmonary Disease, Dis. Chest. **30**:113, 1956.
93. Woodruff, W., Merkel, C. G., and Wright, G. W.: Decisions in Thoracic Surgery as Influenced by the Knowledge of Pulmonary Physiology, J. Thoracic. Surg. **26**:156, 1953.
94. Brinkman, G. L., Raleigh, J. W., and Mitchell, R. S.: The Use of Pneumoperitoneum as an Adjunct to the Prolonged Streptomycin-PAS Treatment of Pulmonary Tuberculosis, Am. Rev. Tuberc. **69**:963, 1954.
95. Williams, J. H., Jr.: The Value of Pneumoperitoneum in Tuberculous Patients Receiving Their First Course of Chemotherapy, Tr. 15th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
96. Moyer, R. E.: Discussion of Williams[95] on Pneumoperitoneum, Tr. 15th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
97. Auerbach, O.: Pulmonary Tuberculosis After the Prolonged Use of Chemotherapy, Am. Rev. Tuberc. **71**:165, 1955.
98. Rafferty, T. N.: Artificial Pneumothorax in Pulmonary Tuberculosis, New York, 1945, Grune & Stratton.
99. Mitchell, R. S.: Artificial Pneumothorax: A Statistical Analysis of 557 Cases Initiated in 1930-1939 and Followed in 1949, Am. Rev. Tuberc. **64**:1, 1951.
100. Foster-Carter, A. F.: Long Term Results of Artificial Pneumothorax Therapy, Brit. M. Bull. **10**:150, 1954.
101. Mitchell, R. S.: Phrenic Nerve Interruption in Treatment of Pulmonary Tuberculosis. I. Statistical Analysis of Results in 398 Patients at Trudeau Sanatorium From 1925 Through November 1947, Am. Rev. Tuberc. **58**:619, 1948.
102. Mitchell, R. S.: Mortality and Relapse of Uncomplicated Advanced Pulmonary Tuberculosis Before Chemotherapy: 1504 Consecutive Admissions Followed 15-25 years. I and II, Am. Rev. Tuberc. **72**:487, 502, 1955.
103. Wilson, N. J., Armada, O., Vindzberg, W. V., and O'Brien, W. B.: Extraperiosteal Plombage Thoracoplasty. Operative Technique and Results With 161 Cases With Unilateral Surgical Problems, J. Thoracic. Surg. To be published.

OL.
4
956

104. Chamberlain, J. M., Storey, C. F., Klopstock, R., and Daniels, C. F.: Segmental Resection for Pulmonary Tuberculosis, J. Thoracic Surg. **26**:471, 1953.
105. Murphy, J. D., and Davis, J. M.: Pulmonary Resection for Tuberculosis: a 5-10 Year Follow-up Study, Tr. 15th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
106. Holland, R. H., Bell, J. W., and Welles, E. S.: Pulmonary Resection in Active Cavitary (Open Positive) Tuberculosis, J. Thoracic Surg. **31**:83, 1956.
107. Raleigh, J. W.: Resections for Closed Lesions, Tr. 15th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
108. Mitchell, R. S.: The Chemotherapy of Pulmonary Tuberculosis, Am. Pract. and Digest Treat. **6**:1855, 1955.
109. Mendenhall, J. T., and Young, W. P.: Localized Resection of Persistent Cavities Within Extensive Diseased Living Tissue—a Follow-up Study, Tr. 15th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
110. Head, J. R.: A Reevaluation of Skin Flap Cavernectomy and Intracavitary Suction in the Light of Modern Drug Therapy in Pulmonary Tuberculosis, Quart. Bull. Northwestern Univ. M. School **29**:355, 1955.
111. Woodruff, W., Kelley, W. O., and Stranahan, A.: Review of Seven Years' Experience With Intracavitary (Monaldi) Drainage of Tuberculous Cavities, J. Thoracic Surg. **18**:777, 1949.
112. Savage, T., and Fleming, H. A.: Decortication of the Lung in Tuberculous Disease, Thorax, **10**:293, 1955.
113. Bauer, H., Robins, M., Sachs, R., and Cummings, M. M: Tuberculous Pericarditis in Veterans, Tr. 15th Veterans Administration-Armed Forces Conf. on the Chemotherapy of Tuberculosis, St. Louis, Feb., 1956.
114. Hardy, K. L., and Sampson, P. C.: The "Quiescent" Tuberculous Bronchus. A Review With a Study of Its Surgical Connotations, Am. Rev. Tuberc. **73**:451, 1956.
115. Chapman, P.: Bone and Joint Tuberculosis. To be published.
116. Schaefer, G.: Female Genital Tuberculosis, Obst. & Gynec. Surv. **8**:461, 1953.
117. Lattimer, J. K.: The Treatment of Tuberculous Infections of the Genitourinary Tract, J. Urol. **74**:291, 1955.
118. Spengler, J. R., and Wilkie, J. M.: Therapeutic Trends in Lymph Node Tuberculosis, Wisconsin M. J. **55**:157, 1956.
119. Mitchell, R. S., and Bristol, L. W.: Intestinal Tuberculosis: an Analysis of 346 Cases Diagnosed on Routine Intestinal Radiography on 5529 Admissions for Pulmonary Tuberculosis 1924-49, Am. J. M. Sc. **227**:241, 1954.
120. Dorkan, N.: Primary Tuberculosis of the Stomach Associated With Intestinal Pneumatosis, J. Internat. Coll. Surgeons **24**:100, 1955.
121. Boucot, K. R., Cooper, D. A., Dillon, E. S., Meier, P., and Richardson, R.: Tuberculosis Among Diabetics: The Philadelphia Survey, Am. Rev. Tuberc. **65**: supplement, Jan., 1952.
122. Gardner, L. U.: The Medical Control of Silicosis and Tuberculo-silicosis, Surg., Gynec. and Obst. **68**:579, 1939.
123. Newman, R. W., Huggin, P. M., Butler, C. L., and Bowman, M. C.: Surgical Therapy in Tuberculosis Complicated With Pulmonary Emphysema, J. Thoracic Surg. **31**:125, 1956.
124. Cohen, J. D., Patton, E. A., and Badger, T. L.: The Tuberculous Mother: 5- to 20-Year Follow-up of 149 Women With 401 Full-Term Pregnancies, Am. Rev. Tuberc. **65**:1, 1952.
125. Mitchell, R. S.: Late Results of Modified Bed Rest in Active Uncomplicated Minimal Pulmonary Tuberculosis, Am. Rev. Tuberc. **67**:401, 1953.
126. Lincoln, N. S., Bosworth, E. B., and Alling, D. W.: The After-history of Pulmonary Tuberculosis. III. Minimal Tuberculosis, Am. Rev. Tuberc. **70**:15, 1954.
127. Alling, D. W., Bosworth, E. B., and Lincoln, N. S.: The After-history of Pulmonary Tuberculosis: V. Moderately Advanced Tuberculosis, Am. Rev. Tuberc. **71**:519, 1955.
128. Alling, D. W., Lincoln, N. S., and Bosworth, E. B.: The After-history of Pulmonary Tuberculosis: IV. Far Advanced Tuberculosis, Am. Rev. Tuberc. **70**:995, 1954.
129. Zahn, D.: Unpublished data.

VOL 4 195

OL.
4
956

Editorials

NEW ORALLY EFFECTIVE ADJUVANTS IN THE MANAGEMENT OF DIABETES MELLITUS

In the thirty-five years which have elapsed since the successful preparation of a crude extract of pancreatic islet tissue by Banting and Best,[1] the subsequently purified and modified insulins have provided fairly satisfactory parenteral substitution therapy for the diabetic patient. The crystalline and retarded action insulins permit great flexibility and fair accuracy of adjustment to the dietary patterns and metabolic requirement of the majority of patients requiring exogenous insulin therapy. It is not unreasonable to hope that a repository injectable insulin preparation capable of acting only on the occasion of physiologic demand can ultimately be developed. Such a development is by no means imminent. However, the diabetic patient, once restored to essentially normal health by insulin therapy, is often prone to regard his dependence on injections and adherence to the discipline of dietary restriction, sterile handling of syringe and needles, etc., as a source of discomfort and frustration. Not a few diabetics, lacking the mental and emotional caliber necessary to the intelligent self-management of their disease, fail to comply with or accept the advices necessary to careful control. On the other hand, our known diabetic population, which comprises about 1 per cent of the United States population and is estimated to increase at the rate of some 50,000 per year, appears to have caused insulin manufacturers some concern lest growing insulin demand exceed the available pancreas gland supply.[2,3]

These many considerations have fostered research efforts to develop an orally effective insulin or insulin substitute. Attempts to protect orally administered insulin from inactivation in the gastrointestinal juices by combination with certain dyes, quinine, etc., have been discouraging. Administration of the hormone sublingually, percutaneously, by inhalation, or in the form of rectal suppositories has been wasteful, impractical, and productive of insignificant or unpredictable response.

Prompted by the hypothesis that wherever carbohydrate synthesis or utilization occurs in nature there must also be present a principle or hormone with insulin-like activity, many have sought for insulinoid substances in extracts of bacteria, yeasts, plants, and cereal grains. J. J. Lewis' thorough review of the literature since 1900[4] attests to the exhaustive and generally unavailing results of these studies. Indeed, some vegetable "insulinoids" undoubtedly

reduced blood sugar concentrations and glycosuria either through an anorexic and emetic action or by toxic effect upon the liver.

The observations by Watanabe,[5] in 1918, that guanidine exerted a blood sugar lowering effect in rabbits prompted Frank, Nothmann, and Wagner[6] to employ guanidine derivatives devoid of neurotoxicity. In 1926, Frank reported the use of decamethylene diguanidine (Synthalin) in diabetes, with relief of symptoms after 100 mg. daily for several days. Synthalin, which had a less potent but more prolonged action than insulin, soon fell into disrepute and was abandoned, for its continued administration was accompanied by gastrointestinal disturbances, hepatic functional derangement with glycogen depletion, icterus, and acute nephritis. Hepatotoxicity in particular appeared to parallel its hypoglycemic action.[7]

The most promising developments in the quest for an orally effective insulinoid substance were happened upon by accident rather than design some fourteen years ago, yet the import of these observations was not fully realized until recently. According to Loubatières,[8,9] it was early in 1942 that Janbon and his associates, while investigating the chemotherapeutic activity of para-amino-benzene-sulfonamido-isopropyl-thiodiazol (2254RP) in typhoid fever, noted the occurrence of reactions following administration of the drug. Loubatières recognized a parallelism between the action of the sulfanilamide derivative and the effects of insulin overdosage and readily confirmed his suspicion in intact fasted dogs. Janbon found that the 2254RP-induced hypoglycemia could be readily corrected by early administration of glucose; if such therapeutic intervention was delayed for several hours in these undernourished patients, irreversible and even fatal neurologic complications resulted. Loubatières[8] then undertook an extensive study of the pharmacology and mechanism of action of 2254RP in dogs and rabbits from 1942 to 1946. He noted that a dose of 0.4 to 1.0 Gm. per kilogram by mouth was sufficient to cause a decrease in blood glucose of 30 to 60 per cent in the fasting intact dog. The oral, intravenous, or intramuscular administration of 2254RP or its sodium salt was without effect upon the level of blood sugar in the totally depancreatized animal. If as little as 1 per cent of the pancreas remained at the juncture of the pancreatic duct and duodenum, the oral administration produced a definite reduction of blood sugar level, producing a rise in respiratory quotient if glucose was administered simultaneously. No alteration in respiratory quotient could be elicited in the totally depancreatized animal by 2254RP alone or during glucose absorption. Atropinization or section of the vagus nerves failed to alter the hypoglycemic action of 2254RP in the dog. Dogs treated with this compound after a four-day period of starvation were found to exhibit as much as a tenfold increase in liver glycogen deposition, in contrast to the marked glycogenolytic action of Synthalin. Inhibition by 2254RP of the "diabetogenic" action of bovine anterior pituitary extract could not be demonstrated.

According to Loubatières,[8] LaBarre and Reuse confirmed the hypoglycemic action of 2254RP in the normal animal and found a more marked and prolonged effect in the adrenalectomized animal. They found the drug to be without hypoglycemic effect in the severely alloxan-diabetic dog. Chen, Anderson,

and Maze,[10] following up the experience of the French, found that a close relative of the sulfanilamide derivative 2254RP, 2-sulfanilamido-5-cyclopropyl-1,3,4-thiodiazol, produced marked hypoglycemia after oral administration in the intact rabbit, while a pronounced hyperglycemia attended its administration in the alloxan-diabetic preparation. While only slightly toxic in rabbits, long-continued administration in rats resulted in goiter formation.[8] It was concluded that this compound, like 2254RP, exerted its hypoglycemic effects by stimulating insulin secretion. Loubatières found that eleven other congeners of 2254RP exhibited varying degrees of hypoglycemic action in the dog and rabbit.

It is curious that the observations of Loubatières and his associates failed to attract more attention in this country and that the French failed to take the initiative in extending their observations to the diabetic patient. The lack of interest in these compounds may have resulted from limited dissemination of French publications during the war years, although Houssay[11] published a careful review of the drugs in 1950.

VOL.
4
1956

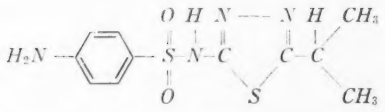
Credit for the current interest in the antihyperglycemic sulfonamide derivatives rests with J. Fuchs, a young resident physician at the Auguste-Viktoria Hospital, Berlin, who was engaged in a clinical study of the antibacterial activity of the Boehringer compound, BZ 55* (para-amino-benzene-sulfonamido-butylurea). Fuchs had noted that certain patients under treatment with BZ 55 exhibited symptoms reminiscent of an insulin reaction, with marked fatigue, psychic disturbances, sweating, and trembling. Study in normal subjects indicated that these effects were associated with a fall in blood sugar concentration. The subsequent publications by Franke and Fuchs[12] and by Bertram, Bendfeldt, and Otto[13] indicated that the oral administration of carbutamide effectively replaced exogenous insulin requirements in many adult diabetic patients and appeared to correct the hyperglycemia and glycosuria of many patients maintained on caloric restriction alone.

Meanwhile, a second aryl sulfonylurea of interest appeared upon the scene. Compound D 860, originated by Farbwerke Hoechst and known as tolbutamide or Orinase in the United States differs from the former compound in that while it is a sulfonamide it is not a sulfanilamide derivative or "sulfa drug." In the parlance of chemist and physician, the term "sulfa drug" has become synonymous with bacteriostatic compounds having the para-amino-benzene-sulfonamide structure.

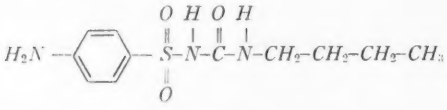
Chemically, Orinase differs from these compounds primarily in the substitution of a methyl group for the para-amino group (Fig. 1).

In considering the chemistry of sulfanilamide derivatives of value clinically, it has been noted that the compounds of importance as bacteriostatic agents contain a nitrogen, nitro, amino, or substituted amino group in the para position of the benzene ring. Replacing the amino group on the benzene ring with $-H$, $-OH$, $-COOH$, $-SO_2NH_2$, an alkyl or a halogen practically destroys bacteriostatic activity, which has been the prime characteristic of these compounds.[14]

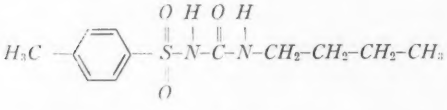
*The generic term carbutamide has been approved for compound BZ 55 (1-butyl-3-p-amino-benzenesulfonylurea) by the Council on Pharmacy and Chemistry of the American Medical Association. The generic name for compound D 860 (1-butyl-3-p-tolylsulfonylurea), or Orinase, is tolbutamide.



para-amino-benzene-sulfonamido-isopropyl-thiodiazol
(2254RP)



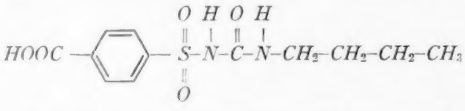
para-amino-benzene-sulfonamido-butyl-urea
(BZ 55, carbutamide)



para-methyl-phenyl-sulfonamido-butyl-urea
(D 860, tolbutamide, Orinase)

Fig. 1.

Loubatières discovered that benzene-sulfanilamido-isopropyl-thiodiazol, which differs from 2254RP by the absence of a para-amino group, has no hypoglycemic activity. Orinase is unique in that its sole pharmacologic action is that of blood sugar depression. It is bacteriostatically inert,[15] and devoid of goitrogenic activity in the laboratory animal.[16] Unlike the "sulfa drugs" it cannot be measured in body fluids by the method of Bratton and Marshall. It cannot be acetylated. The urinary excretory product of Orinase appears almost entirely as the para-carboxy-benzene-sulfonamido-butylurea (Fig. 2) and is without detectable metabolic effect after oral administration to the dog and rat or following parenteral or oral dosage in man.[17a] Because of the extreme solubility of this excretory product of Orinase, crystalluria appears very unlikely.[17b]



para-carboxy-benzene-sulfonamido-butyl-urea

Fig. 2.

Franke and Fuchs,[12] in a study of more than 50 diabetic patients, demonstrated the antihyperglycemic and antiglycosuric action of BZ 55 in about 80 per cent of their series. Most of these subjects had mild diabetes although a few were regarded as having moderately severe disease requiring up to 40 units of insulin per day. Bertram, Bendfeldt, and Otto employed the drug in both juvenile and maturity-onset type diabetics, some of whom required as much as 88 units of insulin daily. Only one of ten juvenile diabetics chosen for study,

a 17-year-old boy with diabetes of three weeks' duration, exhibited any appreciable response to BZ 55 in that its adjuvant use permitted a reduction of the daily insulin requirement from 48 to 24 units. It is recognized that spontaneous variation in insulin requirement, so common in early, unestablished juvenile diabetes, may have accounted for the reduction in his insulin requirement. A few of the other juvenile diabetics exhibited characteristic hypoglycemic reactions during the first two days after institution of combined BZ 55 and insulin therapy; however, the insulin requirement could not subsequently be lowered by continued adjuvant use of BZ 55.

Twenty-five of 28 adult diabetics, aged 49 to 77 years, who were not receiving insulin, exhibited dramatic response within two to five days after start of BZ 55 therapy. None of these was prone to acidosis, but all, according to Bertram, were valid candidates for insulin administration. A daily maintenance dose of 1 Gm. of the drug not infrequently resulted in a fall of blood sugar levels from 300 mg. per cent to 120 – 130 mg. per cent, while glycosuria decreased from 80 to 100 Gm. daily to between 1 and 5 Gm. in the course of several days treatment. Complete insulin replacement was effected in 28 of 38 insulin-requiring diabetics ranging in age from 41 to 77 years. However, 3 patients with mild acidosis received as much as 5 Gm. of BZ 55 daily for several days without evidence of improvement in blood sugar concentration, glycosuria, or acetonuria. No diabetics in severe acidosis were studied by Bertram.

Bertram concluded that diabetics above the age of 45 years, regardless of the severity of their disease, were candidates for sulfonylurea therapy provided their illness was of less than ten years' duration or that they had not received insulin for more than two years. Duration of diabetes and insulin therapy was regarded as an important limiting factor in predicting success of oral drug therapy, while its use was considered to be absolutely contraindicated in diabetic coma, acidosis, surgery, trauma, or in the face of acute febrile infections.

The skepticism which first greeted these reports in the United States, engendered by the earlier tragic history of Synthalin and certain vegetable insulinoids, was rapidly dissipated in the course of careful toxicologic studies and cautious clinical trials by American investigators. Mirsky and his associates[18] demonstrated that the oral administration of tolbutamide (Orinase) in a dose of 50 mg. per kilogram of body weight produced a rapid and dramatic blood sugar depression within thirty minutes to one hour in healthy adult subjects. A secondary rise in blood sugar values followed, but levels remained well below the fasting concentration for five hours. This response was found to be identical with that obtained following the intravenous administration of 0.1 unit of insulin per kilogram of body weight. In a subsequent study by Mirsky, Diengott, and Dolger,[19] 44 patients between the ages of 21 and 73 with a history of insulin-requiring diabetes of one to thirty years' duration were given a similar test dose of tolbutamide after an overnight fast and withdrawal of insulin. A statistically significant, slowly progressive decrease of blood sugar occurred over a period of five hours in all but 10 subjects. Five of these latter 10 exhibited no response and 5 showed only negligible blood sugar decrease. In contrast, 24 control subjects given sodium bicarbonate solution exhibited mild blood sugar elevation.

Other modifications of this single dose test are currently under study as screening procedures for response to sulfonylurea therapy and will be published shortly.

In further confirmation of the German reports, Miller and Craig[20] reported the instance of a 54-year-old obese female diabetic with stable diabetes of twenty years' duration who had taken a minimum of 45 units of insulin daily for the past five years. Insulin withdrawal resulted in a rise of fasting blood glucose values of from 180 mg. per cent to levels of between 259 and 300 mg. per cent during the control period. When maintained on a 1,250 calorie diet, glycosuria varied between 17 and 48 Gm. daily. The morning after an initial 3.0 Gm. dose of tolbutamide, the fasting blood glucose was 171 mg. per cent. After ten days on a daily maintenance dose of 2.0 Gm. of the drug, the fasting blood sugar had fallen to 127 mg. per cent, while urinary glucose excretion amounted to 1.0 Gm. daily. Substitution of placebo tablets resulted in prompt return of hyperglycemia and glycosuria. Reinstitution of tolbutamide therapy was accompanied by satisfactory reduction of blood and urinary glucose concentrations except for temporary mild metabolic decompensation during a surgical procedure.

Dolger[21] has observed the response to tolbutamide in 200 diabetic subjects treated for several months. Patients whose diabetes presented before the twentieth year of age could not be controlled on tolbutamide, while 40 per cent (7 of 18 patients) of those whose diabetes had its onset between the ages of 20 and 40 years achieved excellent control with the sulfonylurea. The most striking success was attained in those in whom the onset of diatetes occurred after the age of 40 years, in Dolger's study. Of a group of 91 diabetics of the maturity-onset group, 82 were successfully controlled on tolbutamide while 9 were regarded as failures. Forty-four of these patients, whose daily insulin requirements ranged from 10 to 100 units, no longer required routine exogenous hormone therapy, while the insulin requirement of 6 others was reduced by one-third to one-half. The remaining 32 patients, whose diabetes was managed solely by caloric restriction, achieved more uniform control of blood glucose levels and glycosuria on sulfonylurea therapy than was possible on diet alone. Dolger confirms the German observation that aryl sulfonylurea therapy is of little or no value in the management of diabetes presenting before the age of 20 years. However, contrary to the opinion of Bertram and associates, he finds no correlation between response to the sulfonylureas and duration of diabetes, duration or dosage of insulin, or obesity or leanness in diabetics whose metabolic syndrome developed after the age of 40 years.

Carbutamide and tolbutamide are equipotent as blood sugar decreasing agents.[22] Clinical experience in Germany and the United States indicates that patients responsive to a test dose of the aryl sulfonylureas can be started on therapy with a dose of 2.5 to 3.0 Gm. on the first day, 2 Gm. on the second day, and 1 Gm. daily thereafter. The ultimate maintenance dose may be as little as 0.5 Gm. or as much as 2 Gm. per day, rarely higher. When initiating therapy in patients heretofore managed by diet restriction alone, it has been the practice of some German investigators[22] to follow the above regimen, administering the drug in divided doses with or after meals, or as a single dose each morning. In those whose insulin requirement is 20 units per day or less, insulin therapy may

VOL. 4 1956

be stopped abruptly and oral drug therapy may be instituted directly. Those patients whose insulin requirement is between 20 and 40 units per day are initiated to aryl sulfonylurea therapy with a concurrent 50 per cent reduction in insulin, with further daily reduction of the insulin as oral therapy is continued. In those patients accustomed to larger daily insulin requirements, sulfonylurea therapy may be given in conjunction with a 20 per cent reduction of the usual insulin dose in the first day, with further careful reduction in hormone dosage on successive days. The too rapid conversion from insulin to aryl sulfonylurea therapy may result in decompensation of the diabetes even in persons whose whose insulin requirement has been small. Occasional hypoglycemic reactions may occur during the period of conversion but can be readily corrected by the administration of glucose. The routine use of a single test dose of one of the aryl sulfonylureas appears to be a highly satisfactory method for selection of cases responsive to oral management.

It must be emphasized that while the aryl sulfonylureas abolish or largely reduce glycosuria and produce a state of normoglycemia with the absence of diabetic symptoms in a large number of diabetic patients, *they are not true substitutes for insulin.* They appear to make unnecessary the routine use of insulin in the management of uncomplicated diabetes of mild or moderately severe degree. They appear to be of no value in juvenile diabetes nor can they be used in the treatment of the life threatening complications of diabetes-coma, acidosis, acute febrile illness, severe trauma, or surgical procedures. Here, insulin is indispensable.

The clinical experience which has already accrued with these compounds indicates that complications attendant upon their use are probably not frequent. Bertram and his associates[13] mention that jaundice occurred in one patient on the tenth day of BZ 55 therapy; however, prodromal symptoms suggestive of infectious hepatitis existed prior to institution of carbutamide therapy. Mohnike and Stötter[22] reported two instances of hepatocellular jaundice in a review of 781 patients treated with tolbutamide in five German clinics. One of these occurred fourteen days after cessation of tolbutamide therapy while the other occurred in the course of treatment. The German authors could not attribute the development of hepatitis to tolbutamide therapy in these cases. Except for the above-mentioned instances of clinical jaundice, the German authors failed to find laboratory evidence of hepatic functional derangement on tolbutamide therapy in their series.[22]

Ridolfo and Kirtley[24] reported that only one in their series of 31 patients exhibited evidence of toxicity to BZ 55 administration. Mental clouding occurred in this patient in association with elevated blood carbutamide levels; however, improvement occurred when BZ 55 dosage was lowered. A skin rash and leukopenia developed in the same patient after three months of therapy on a dose of 1.0 Gm. daily. The rash disappeared and white blood cell count returned to normal on the eleventh day after cessation of BZ 55 therapy. No alteration of blood or bone marrow elements or disturbance of blood coagulation systems was found in the German study of 781 patients on tolbutamide therapy.[22] Urticaria and morbilliform eruptions have been cited on occasion and appear

to be less commonly associated with one compound than the other.[22] Minor digestive disturbances and headache may occur, especially when large doses of the aryl sulfonylureas are employed. Renal toxicity has not been reported. *The safety of long-term use of these agents cannot be predicted at this time, as is the case with any newly introduced series of therapeutic agents.*

An exhaustive investigation of the behavior of these agents over the past year has been under way, yet their mechanism of action remains unknown. However, it is of some interest to recall that the mechanism of action of insulin remains to be explained after more than thirty years of investigation. In contrast to insulin, however, the aryl sulfonylureas are without effect in depancreatized, eviscerate, or severely alloxan-diabetic animals. They appear to act only in the presence of a functioning source of endogenous insulin and may exert some sparing action on the exogenously administered hormone. Some attribute their action to an inhibitory effect upon insulinase, others to an action upon enzyme systems involved in hepatic carbohydrate metabolism. Mirsky and his associates[23] feel that the hypoglycemic action of the aryl sulfonylureas may be due to an inhibitory effect upon hepatic insulinase. Vaughan,[25] could not demonstrate insulinase inhibition when Orinase was added to incubated rat and rabbit liver slices in concentrations which produce hypoglycemia in vivo. However, the tolbutamide concentrations employed by Vaughan appeared to diminish epinephrine-induced glucose release from liver slices. While these drugs depress total glucose-6-phosphatase activity of the liver,[26] Berthet[27] finds that several sulfonamide compounds lacking hypoglycemic activity also exhibit this effect. A damaging effect upon glucagon-secreting tissues of the pancreas has been proposed but strongly contested. Loubatières' early contention that these compounds are insulinogenic, directly stimulating production and release of insulin by the pancreatic β-cells, cannot be dismissed. None of the yet proposed concepts of action of the sulfonylureas has withstood challenge. These issues remain to be clarified.

With the advent of the aryl sulfonylureas, we may be upon the threshold of a new era of therapy in diabetes, for they give promise that a significant portion of our diabetic population may be unshackled from syringe and needle. The clinician concerned with the problems of diabetes, no longer the dour skeptic, has assumed an attitude of cautious enthusiasm about these fascinating compounds, while the curiosity of the fundamental investigator has been further whetted by these new agents in his efforts to better define the nature of this common disease.

REFERENCES

1. Banting, F. G., and Best, C. H.: The Internal Secretion of the Pancreas, J. Lab. & Clin. Med. **7**:251, 1922.
2. Joslin, E. P.: Medical Progress: Diabetes, New England J. Med. **238**:401, 1948.
3. Salter, W. T.: A Textbook of Pharmacology, Philadelphia, 1952, W. B. Saunders Company, p. 587.
4. Lewis, J. J.: Diabetes and the Insulin Administration Problem, Physiol Rev. **29**:75, 1949.
5. Watanabe, S.: Studies in the Metabolic Changes Induced by Administration of Guanidine Bases, J. Biol. Chem. **33**:253, 1918.
6. Frank, E., Nothmann, M., and Wagner, A.: Über die experimentelle und klinische Wirkung des Dodekamethylendiguanids (Synthalin B), Klin. Wchnschr. **7**:1996, 1928.

VOL 4 195

7. Sollmann, T.: A Manuel of Pharmacology, ed. 6, Philadelphia, 1942, W. B. Saunders Company, p. 416.
8. Loubatrières, A.: L'utilization de certaines substances sulfamidées dans traitment du Diabète sucré expérimental. Recherches personnelles (1942-1946), Presse méd. **63**:1701, 1955.
9. Loubatières, A.: Les substances sulfamidées dans le traitement du diabète sucré. Recherches personnelles (1946-1955), Presse méd. **63**:1728, 1955.
10. Chen, K. K., Anderson, R., and Maze, N.: Hypoglycemic Action of Sulfanilamido-cyclopropylthiazole in Rabbits, and its Reversal by Alloxan, Proc. Soc. Exper. Biol. & Med. **63**:483, 1946.
11. Houssay, B. A.: Action of Sulfur Compounds on Carbohydrate Metabolism and on Diabetes, Am. J. M. Sc. **219**:353, 1950.
12. Franke, H., and Fuchs, J.: Ein neues anti-diabetisches Prinzip. Ergebnisse klinischer Untersuchungen, Deutsche med. Wchnschr. **80**:1449, 1955.
13. Bertram, F., Bendfeldt, E., and Otto, H.: Über ein wirksames perorales Antidiabeticum (BZ 55), Deutsche med. Wchnschr. **80**:1455, 1955.
14. Schnitker, M. A.: The Sulfonamide Compounds in the Treatment of Infections, New York, 1942, Oxford University Press, pp. 33-34.
15. Lewis, C.: Department of Infectious Disease Research, The Upjohn Company. (To be published.)
16. Larson, E. J.: Department of Pathology, The Upjohn Company. (To be published.)
17a. Louis, L. H., et al.: The Structure of a Urinary Excretion Product of 1-butyl-3-p-tolylsulfonylurea (Orinase). (In Press.)
17b. Forist, A. A., and Chulski, T.: Department of Physics, The Upjohn Company. Symposium on Sulfonylurea Compounds, Metabolism, November, 1956.
18. Mirsky, I. A., Diengott, D., and Dolger, H.: Differentiation of Diabetes Mellitus Due to Impaired Insulinogenesis From That Due to Increased Insulin Destruction, Read at 28th meeting of the Endocrine Society, June 10, 1956.
19. Mirsky, I. A., Diengott, D., and Dolger, H.: Hypoglycemic Action of Sulfonylureas in Patients With Diabetes Mellitus, Science **123**:583, 1956.
20. Miller, M., and Craig, J. W.: Hypoglycemic Effects of 1-butyl-3-p-Toluene Sulfonylurea Given Orally in Human Diabetic Subjects, Metabolisim **5**:162, 1956.
21. Dolger, H.: Clinical Experience With Orinase, Read at the American Therapeutics Society, Chicago, June 9, 1956.
22. Bander, A., Creutzfeldt, W., Stötter, G., et al.: Über die orale Behandlung des Diabetes mellitus mit N-[4-Methyl-benzolsulfonyl]-N'-butyl-harnstoff (D 860). Klinische und experimentelle Untersuchungen, Deutsche med. Wchnschr. **81**:823, 1956 and **81**:887, 1956.
23. Mirsky, I. A., Peirsutti, G., and Diengott, D.: The Inhibition of Insulinase by Hypoglycemic Sulfonamides, Metabolism **5**:156, 1956.
24. Ridolfo, A. S., and Kirtley, W. R.: Clinical Experiences With Carbutamide, an Orally Given Hypoglycemic Agent, J.A.M.A. **160**:1285, 1956.
25. Vaughan, M.: In Vitro Studies on the Action of Sulfonamide Hypoglycemic Agents, Science **123**:885, 1956.
26. Hawkins, R. D., Ashworth, M. A., and Haist, R. E.: Effect of BZ 55 (Carbutamide) on Glucose-6-Phosphatase Activity, Canad. M.A.J. **74**:972, 1956.
27. Berthet, J., Sutherland, E. W., and Makman, M. H.: Observations on Action of Certain Sulfonylurea Derivatives, Metabolism, November, 1956.

C. J. O'Donovan, M.D.
Department of Clinical Investigation
The Upjohn Company
Kalamazoo, Mich.

OL.
4
956

CANCER REGISTERS

The practice of keeping systematic records on cancer patients has spread rapidly during the past twenty years. Cancer registers are now found in many hospitals and health departments. The requirements set forth by the American College of Surgeons[1] for the approval of a cancer program will encourage still more hospitals to install such registers.

The paper in this issue by Haenszel and Hon[2] distinguishes between the service and research uses of a register. Cancer registers have been able to play a research role because of the emphasis on learning the fate of all diagnosed cases, irrespective of the nature of treatment or of whether any service is rendered to the patient or his family. This statement does not hold true for many registers dealing with other diseases, since inclusion of patients in a register is often determined by program requirements and looked upon as an administrative device for ensuring service.

The service aspects of case registers have been discussed by Bellows.[3] She describes the three main service functions: a control mechanism whereby continuity of service can be maintained; a coordinating reference file; and a source of administrative statistics. The emphasis in administrative statistics should always be directed to the value and efficiency of the program from the standpoint of the patient. These functions include some major objectives of the American College of Surgeons in requiring hospitals to maintain cancer registers as a prerequisite for an approved cancer program. The inclusion of all cases seen in a hospital also permits the staff to use the cancer register in evaluation of therapy.

State cancer registers maintained in some areas could be particularly valuable for research, since they are unaffected by selection factors associated with admission to a single hospital such as those which might arise from the presence of a prominent specialist on the staff. Furthermore, they can cover all diagnosed cases in a known population, which permits the computation of incidence and prevalence rates. However, state registers are not designed to meet the service needs catalogued above. They are too removed from the scene of action, and experience has shown that they are not geared to the identity of individual patients; they deal with statistics, not individuals.

Well-run central cancer registers, useful for research purposes, are expensive. The total annual cost of operating registers meeting good standards in each state would be in the neighborhood of two million dollars. The issue is not whether such sums could be obtained for this purpose, but whether this would be the most advantageous use of such money. If the principle is accepted that state registers are primarily research tools, it follows that they are not needed in all states. As Haenszel and Hon put it, "48 registers would not yield 48 times as much information."

VOL
4
195

It is important to remember that registers are only one tool for the study of cancer or any disease entity. Fruitful work in cancer epidemiology requires a variety of study approaches and calls for a synthesis of findings from analyses of mortality data, retrospective studies of diagnosed cases and matched controls, long-term observation of special groups, morbidity surveys, and application of screening tests, in addition to case registers. The National Cancer Institute, in its intramural research and grants program, has supported studies employing all these diverse approaches.

Individual states should be encouraged to review their resources and to search for promising study situations before committing themselves to a central cancer register. They might find some of the other types of cancer studies more rewarding in the long run.

OL.
4
956

While diversification of study approaches in all parts of the country will provide data which can reinforce and complement one another in building up knowledge about cancer in human populations, there is another principle worthy of application. It follows the military maxim calling for a concentration of force to achieve a break-through to an objective. Because of the great expense entailed by a basic register program, it seems wasteful not to incorporate special, collateral studies as part of the program. Even if special studies doubled or tripled the cost of the central register, the benefits to cancer research would far exceed those to be obtained by duplicating the basic register operations in two or three states. Such a program of special studies built around the central register as a core is being developed by the Connecticut State Department of Health. There is a need for some other states in different regions of the country to sponsor cancer registers oriented to research so that findings may be collated and examined for consistency or for evidence of divergent state or regional patterns.

One limiting factor, at present, to the development of such a program is a shortage of personnel trained in research and having an aptitude for research; namely, epidemiologists and statisticians. More physicians, particularly, are needed. Health agencies interested in undertaking cancer registers emphasizing research should explore avenues of securing supplementary financial and technical support, including training grants for qualified persons who wish to enter this field.

REFERENCES

1. American College of Surgeons: Manual for Cancer Programs (Approved by Committee on Cancer), Chicago, 1953.
2. Haenszel, W., and Hon, N. B.: Case Registers and Other Statistical Approaches to the Study of Cancer, J. CHRON. DIS. **4**:589, 1956.
3. Bellows, M.: Case Registers, Pub. Health Rep. **64**:1148, 1949.

JOHN R. HELLER, M.D.
National Institutes of Health
Bethesda, Md.

THE HEALTHFUL BENEFITS OF STRESS

In the years since World War II much attention has been given to the health damage produced by life stresses. We learned in the war about the exhausting effects of the emotional stresses of combat situations and other types of military experience. We have learned about pathologic effects upon vulnerable organs and tissues when physiologic reactions occurring in stressful life situations exceed healthy limits and thus harm tissues or hinder adaptive physiologic processes. The area of so-called psychosomatic medicine has been extensively surveyed, with many empirical findings indicating the potentialities for bodily harm from miscarried emotional reactions to stress.

It is, of course, a more difficult and a slower task to elucidate the details of the pathogenic processes and recovery processes related to stress. So, in a vague way, stress has become a bad word, in somewhat the same way that the word anxiety has become a bad word in psychopathology. Perspectives have become so distorted at times that health efforts are aimed too sweepingly at the elimination of stress or anxiety. But life without struggle and effort—without stress and anxiety—can be a very stale and meaningless existence.

In dealing with the aged, the chronically ill, and the handicapped, there is some danger that a medical profession too much obsessed with the harmfulness of stress may overlook its beneficial potentialities. It is easier to prohibit stress than to prescribe for it properly; it is also easier to prescribe properly than to fill the prescription. Particularly in urban life there may be a lack of opportunities and challenges to suitable significant activity for elderly people, such as were more abundantly present in our former rural and village way of living. It will take much planning and doing, by volunteer community agencies and devoted people of vision and ingenuity, to develop the means for purposeful and courageous continuation of lives of significant effort among our aging population. There are many who may be handicapped but who should not be shelved by the limitations of chronic illness.

Job retirement, with illness or without, separates one from a sustaining context of activities and meaningful personal relationships. The narrowed circle of contacts, although kind and benevolent, may demand so little response as to leave one feeling unwanted and futile. Individual ingenuity may not be sufficient to devise or discover tasks and problems which sustain one's sense of dignity and worth, particularly when the vague need is not understood or is misunderstood as a tension state, for which more idleness and futility are prescribed.

In modern living, the elderly member of the family without a job or without specific home-keeping responsibilities feels uneasy. Some responsible task or service restores meaning and purpose and may also bring the rewards of appreciative response from others.

VOL
4
195

In many of our states, public sentiment has established and supported hospitals for chronic patients which all too often serve merely to receive and to take care of patients, neglecting the possibilities for rehabilitation and the resumption of a healthy amount and style of stressful living. There is a need—and that need is increasing and sure to increase much more—for sheltered workshops, special industries for handicapped workers, and for volunteer agencies which can find or develop gratifying (and stressful) activities. With such community assets, the chronic disease hospitals may function more effectively and gratifyingly as health centers, prescribing planned and guided rehabilitation, toward zestful and stressful health, rather than debilitating custodial care.

There is great need for enthusiastic leadership and devotion—lay and professional—in such community developments. The doctors should think more discriminatingly about stress—acknowledging and endorsing the health values which are inherent in purposeful personal striving.

John C. Whitehorn, M.D.
Johns Hopkins Hospital
Baltimore, Md.

VOL.
4
1956

THE NATURE OF MEDICAL ERROR

A Study in Applied Medical History

Es irrt der Mensch, so lang er strebt—Goethe

My preparations for this presentation had barely gotten under way when it became clearly apparent that, "like little wanton boys that swim on bladders," I had ventured far beyond my depth. I realized that I had naïvely assumed a truly gigantic task. I shall, therefore, take my lead from the old essayists and ask you to change my title in your minds to read, "Reflections Upon—," or "Notes for a Study of—," or "Random Thoughts Upon—" the nature of medical errors. In this way it will be clear that what I am attempting is merely by way of reconnaissance, rather than a full-scale exploration. I shall be enabled to skip about in the historical periods, indulge in broad generalizations, and to avoid documentation where inconvenient. As a result there will surely be a loss of scholarly qualities, but my reflections may gain somewhat in entertainment and stimulation.

The area to which I wish to direct your attention is that of erroneous medical attitudes. This is a field quite different from diagnostic or therapeutic mistakes made in single cases at the bedside, whether disclosed by subsequent events, or by post-mortem examination. My interest is really epidemiologic, using the word epidemiology in its broad meaning as the study of disease in the aggregate—or as a mass phenomenon, contrasted with clinical medicine which is concerned with sick individuals. The methods that proved so helpful in studying infectious diseases now are being applied to noncommunicable disorders with success. Thus, we hear discussions of the epidemiology of health, of accidents, of old age, and even of gout. We have good ground then for an epidemiology of errors in medical attitudes, and we can find abundant data not only in volumes on medical history and in general histories of the old-fashioned kind that chronicled wars, but also in the newer studies that emphasize the social, economic, and cultural aspects of different periods of our civilization.

Actually, in studying medical error in its broad sense, we are tracing not only medical progress but human progress in general, bearing in mind that an error reaches its full bloom as a dogma, which must be destroyed by bold thinking and sound observation before it is recognized as false teaching. A good diagnostic clue to the existence of error is support of an idea by a long list of seemingly sound reasons with little or no experimental confirmation, and backed by the solid authority of elder statesmen. I hardly need remind you of the famous

Presented at the Twenty-ninth Annual Meeting of the American Association of the History of Medicine, Durham, N.C., April 21, 1956.

VOL
4
195

controversies provoked in this country and in Europe by the independent discoveries of Oliver Wendell Holmes and Ignaz Semelweiss on the contagiousness of childbed fever. Error keeps good company and moves in the best circles. In retrospect, errors seem plausible and we can often, without straining, understand why they were so long accepted. Fifty years ago physicians were taught that in typhoid fever the small intestine is studded with ulcerations. It was therefore clear that these patients could not digest their food and must be fed very sparingly. This seemingly convincing reasoning was dispelled by the actual use of adequate diets by Shattuck in Boston and Coleman at Bellevue Hospital. To everyone's surprise the patients who were thus fed did very well indeed, and it soon became apparent that many of the complications ascribed to the disease were really due to starvation. The doctrine of underfeeding fevers was deeply rooted in medical practice and had persisted in spite of the efforts of the great Irish clinician, Robert James Graves (1796-1853), who requested that his epitaph should read, "He fed fevers."

OL.
4
956

Even more recently we were taught that surgical operations were shocking to the whole body, that wounds must be allowed to heal tightly, and that early movements might spoil the whole procedure. Immobilization after operation was the rule until brave spirits among the surgeons showed that the entire procedure was not only unnecessary but actually harmful. Patients were helped out of bed the same day or the next after operation, voided naturally, had early bowel movements, and regained their strength more rapidly. Thus a sound observation or a carefully planned clinical experiment can quickly slay the dragon of usage and time-honored custom. Looking back, I think we medical men were most horrified at this further example of what sometimes seems like lack of finer feelings in our surgical colleagues. The armchair treatment of heart disease advocated by Dr. Samuel Levine, which followed shortly thereafter, was even more of a shock to a generation of physicians fearful of sudden death in cardiac patients and anxious to avoid being blamed for carelessness by colleagues and patients' families.

These examples from the recent past serve to point up the strong possibility that many of our current practices may well need critical scrutiny. It would be folly indeed for me to belittle the physicians of another day, who did the very best they knew how with the knowledge at hand. I have no desire to stand before you as a sort of elderly Jack Horner pulling medical boners out of an historical pie to proclaim to you how bright we all are. Our studies of the past must be conceived in a spirit of humility, based on the knowledge of our own vulnerability and motivated only by the desire to avoid pitfalls, traps, and hazards that have ensnared our predecessors, our contemporaries, and ourselves.

With full awareness of the dangers of systematization and oversimplification, I am now going to discuss three ways in which erroneous attitudes have developed in the past and continue to flourish in the present. These pathogenetic mechanisms are: first, unquestioning acceptance of authority; second, misapplications or misconstructions of the scientific method; and, third, the influence of emotional attitudes on the thinking of physicians. Overlapping of these categories is at once apparent, and, in fact, the third may be construed in such a

way as to encompass the first two. I think, however, that appropriate illustrations may clarify my thinking for you and help you to set up your own categories, if these suggestions of mine are found wanting.

The best example of abject submission to authority is to be found in the effect of Galen, the great Greek physician, upon the development of medicine. While his positive contributions were many and varied, and his writings voluminous, he was cocksure, glib, and highly theoretical. Garrison's summation[1] is most instructive: "The effect of this dogmatism and infallibility upon aftertime was appalling; for while Galen's monotheism and piety appealed to the Moslems, his assumption of omniscience was specially adapted to appease the mental indolence and flatter the complacency of those who were swayed entirely by reverence of authority. Up to the time of Vesalius, European medicine was one vast *argumentum ad hominem* in which everything relating to anatomy and physiology as well as disease was referred back to Galen as a final authority from whom there could be no appeal. After his death, European medicine remained at a dead level for nearly fourteen centuries." For the study of patients, advocated by the Greeks of the Hippocratic School, Galen's followers substituted the study of books, a practice that became general in all branches of learning throughout the Middle Ages. The movement we now know as the Renaissance began with the migration to Italy of Greek scholars following the fall of Constantinople in 1453. Gradually, scholars in Western Europe learned to read Greek classics in the original, but in 1500, when Erasmus came to Oxford, there was no one there to teach him the Hellenic language. Today, we still honor the teachings of Hippocrates and place observation of actual patients as the basis of sound medical thinking. We prize books highly for their ability to transmit widely and cheaply the thoughts of writers everywhere, whether contemporary or of a bygone day. The original sources are so numerous that we can hardly hope to read more than those in some limited specific field, and we naturally welcome the condensations of past and present experience that constitute our textbooks and our didactic lectures. I may add in passing that my aversion to bibliolatry includes the "Great Books" system of education.

The example of Galen is so remote that one might think that such unquestioning submission to authority is really a thing of the past. Unfortunately, this is a recurrent error in every generation because authoritative figures and institutions gain great influence, and their followers often accept their dicta simply because of their faith in the wisdom of the teacher. This lesson I learned early in my carrer. When I was a fourth year student in 1917, we were taught that postpneumonic empyema should be drained surgically as soon as bacteria could be found in the pleural fluid. Within less than a year I found myself in the United States Army serving as pathologist to the Empyema Commission at Camp Lee, Virginia. This group was headed by Dr. E. K. Dunham, and included Evarts Graham, Thomas Rivers, Clifford Hartman, A. V. Moschcowitz, Kenneth Maxcy, Ralph Kinsella, and Frederic P. Gay. The Commission was directed to study the treatment of empyema complicating the streptococcus pneumonias following measles, because under the doctrine of early operation the death rate was alarmingly high. The Commission established through its

VOL
4
195

work important principles that made clear the necessity for delaying operation as long as possible, until the mediastinum became fixed and the patient's underlying infection brought under control. Today, when empyema is a rare complication of a disease no longer feared, it is difficult to realize how completely the Commission's findings upset the currently accepted procedures, based on high authority.

In the study of poliomyelitis, the leading investigatiors insisted for years on the nasal spread of the disease and denied vehemently any possibility of gastrointestinal involvement. Thirty years passed before the presence of virus in the stools was demonstrated and only then did it become clear that the original investigators had examined the excreta only a few times with negative results.

In the application of the scientific method to the problems of medicine, the possible errors are infinite, whether they be in observation, in correlation, in formulation, or in experimental proof of hypotheses. A recent study by Ross[2] on the use of controls in medical research was based on a review of one hundred consecutive and unselected current medical journal articles describing some procedure or therapy for disease. In 45 per cent of these papers the investigators made no attempt to compare results of the specific therapy described to those in an untreated group. Eighteen per cent more used controls considered inadequate. In commenting on his findings, Ross emphasized the necessity of maintaining a sceptical attitude toward all reports, however enthusiastic, unless the personal bias of the investigator and the variability of the disease itself were corrected for by setting up rigid controls. Of course, there is also an implied criticism of editorial acumen because all of the papers studied appeared in first-rate journals.

The method of clinical-pathologic correlation is basic in teaching and in research, but medical history furnishes examples of errors on the part of famous pathologists which had widespread effects. I refer particularly to the views of Rokitansky and Virchow, who both "regarded fibrosis of the myocardium with its aneurysmal bulgings as inflammatory in origin and overlooked the part played by the sclerosed coronaries in bringing about these conditions in the wall of the heart."[3] These authoritarian misinterpretations persisted for many years until the pathologic pictures were clarified by Weigert and Ziegler.

The entire story of the development of our knowledge of coronary heart disease is incredibly confusing because of difficulties in communication, because of a bewildering terminology, and because of the slowness of certain authorities to grasp the meaning of clinical observations. In it we find many varieties of medical error. In 1778, John Fothergill's patient with angina was examined after death by John Hunter and found to have bony-hard coronaries. In 1793, Hunter himself died after years of anginal pain, and at the autopsy performed by Jenner, ossified coronaries were found, as had been predicted before death by Jenner and his friend Caleb Parry. In spite of these clear correlations and in spite of isolated well-informed clinicians, such as von Leyden and Huchard, the whole matter remained confused until 1912, when Herrick[4] published "Clinical Features of Sudden Obstruction of the Coronary Arteries." From this paper dates our modern understanding of the subject, because the fine observations

of others were overlooked or failed to impress. Dr. George Dock,[5] then of the University of Michigan, had reported four cases of coronary thrombosis in 1896, including one male patient of 36 years in whom the correct diagnosis was made during life. Adam Hammer,[6] an Austrian physician, practicing in St. Louis, had made an ante-mortem diagnosis of coronary thrombosis confirmed at post-mortem. His report appeared in the *Wiener Medizinische Wochenschrift* in 1878 and went unnoticed until years later. Herrick[7] himself has amplified a statement of Sternberg: "The unity of coronary disease was obscured for nearly a century because the effects of such disease were often hidden under a variety of misleading captions—angina pectoris, cardiac neuroses, infarct of the myocardium, rupture of the heart, acute and chronic myocarditis, acute and chronic heart failure, fatty degeneration, partial aneurysm of the heart, pericarditis."

In spite of all this, certain die-hard authorities still clung to their theories. On May 5, 1924, the famous Professor Karl F. Wenckebach of Vienna lectured at the Royal College of Physicians of London on "Angina Pectoris and the Possibilities of Surgical Relief," denying the relationship to coronary artery disease. In discussing this paper, the "truly distinguished octogenarian" Sir Clifford Allbutt expressed his satisfaction that "certain hypotheses which I have propounded to rather deaf ears for five and thirty years have received confirmation from a supreme judge."[8] Allbutt was Regius Professor of Medicine at Cambridge, a fine speaker, a profound classical scholar, and, before going to London, had conducted an active medical practice in Leeds. He had made many important contributions to medicine and his views on angina pectoris carried great weight in Britain. The historians of the future may have the same difficulty in understanding our present confusion about hypertension and arteriosclerosis.

Consideration of the effect of emotional attitudes on the thinking of physicians naturally should include the influence of aging, of personal rivalries, and of the need to maintain face. At this time I wish only to mention the neglect of certain diseases regarded as loathsome and of diseases in unpleasant areas such as the rectum and anus. Long-standing neglect of chronic disabling conditions, such as hemiplegia, is gradually being overcome by the enthusiasm of workers in rehabilitation. Worthy of more extended comment is the effect of the physician's enthusiasm for a particular procedure upon his patients and upon his own interpretation of his findings, which has been so well brought out by Beecher's work.[9] Here, too, we must mention the frustration that arises from lack of knowledge and understanding. This is the cause of the disinterest manifested by many physicians in the maladies of aged men and women, but more particularly is the basis of the difficulty experienced in comprehending disorders of the mind.

Zilboorg and Henry[10] have summarized this aspect with great clarity, in covering centuries of history. "In order to identify one's self with a mentally sick patient a totally different set of psychological reactions is required of the doctor. Every mental patient presents some form of unwillingness or inability to accept life as it is. Every mental patient either aggressively rejects life as

VOL 4 195

we like it—and he therefore was thought of as an heretic, witch or sorcerer—or passively succumbs to his inability to accept life as we see it—and he therefore was called bewitched. In the mind of the mentally healthy man, including the medical man, a mentally ill person still appears as an adamant rebel against our cultural common sense, or as a weakling who gives in to forces other than our common sense. Mental illness requires a singularly humanistic tolerance on the part of the doctor, without which a proper identification with the patient cannot be made."

In spite of vigorous teaching to the contrary, the old separation of mind and body backed by ecclestiastic authority still persists, and the terminology based on this division is distressingly current. We still hear physicians describing diseases as "physical," "mental," "psychic," "somatic," "organic," "functional." Cobb has stated, "One must put aside superstition, mythology, parallelism and other outworn creeds, and accept simply the fact that all stimuli which play on an organism are physical, that all phenomena which take place in organs are organic and that the psychologic processes although the most complex are not exceptions."

OL.
4
956

Much of the early reaction against psychoanalysis and of that which still persists in certain quarters was due to Freud's invasion of areas long protected by strong taboos. The work of Hans Selye and of Harold Wolff in clarifying the mechanisms by which emotional stresses affect physiologic processes is gradually breaking down long-existing barriers. Broadening the base of medical teaching to include normal psychologic development, initiated by Adolf Meyer over fifty years ago, will eventually produce a generation of physicians better equipped to handle the everyday problems of human beings that are not reflected in physical signs or laboratory findings. Medical schools are beginning to emphasize the importance of social and economic factors in disease. The number of qualified psychiatrists is gradually increasing in response to a great need, but medical educators today realize that the real aim must be to put more psychiatric understanding and knowledge into the equipment of all practitioners and all specialists, no matter what their field.

This tentative effort at analyzing the nature of persistent erroneous medical attitudes has suggested three large areas of causation, namely, the unquestioning acceptance of authority, the misuse of the scientific method, and the effect of emotional attitudes on the thinking of physicians. Examples cited emphasize that these causes are operative today as in the recent and remote past. Further study should develop these principles to the point where medical teachers both in the basic sciences and in the clinical branches can utilize medical history to inculcate in their students a healthy scepticism, a sound understanding of methodology, and the cultivation of objectivity.

REFERENCES

1. Garrison, F. H.: An Introduction to the History of Medicine, ed. 4, Philadelphia, 1929, W.B. Saunders Company, p. 112.
2. Ross, O. B., Jr.: Use of Controls in Medical Research, J.A.M.A. **145**:72, 1951.
3. Herrick, J. B.: A Short History of Cardiology, Springfield, 1942, Charles C Thomas, p. 214.
4. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J.A.M.A. **59**:2015, 1912.

5. Dock, G.: Some Notes on the Coronary Arteries, Med. & Surg. Reporter, Phila. **75:1**, 1896.
6. Hammer, A.: Ein Fall von thrombotischen Verschlusse einer der Kranzarterien des Herzens, Wien. med. Wchnschr. **28:**97, 1878.
7. Herrick, J. B.: A Short History of Cardiology, Springfield, 1942, Charles C Thomas, p. 227.
8. Rolleston, H. D.: The Right Honourable Sir Thomas Clifford Albutt, a Memoir, London, 1929, The Macmillan Company, p. 285.
9. Beecher, H.: The Subjective Response and Reaction to Sensation, Am. J. Med. **20:**107, 1956.
10. Zilboorg, G., and Henry, G.: A History of Medical Psychology, New York, 1941, W. W. Norton & Company, p. 523.

FREDERIC D. ZEMAN, M.D.
111 East 88th St.
New York 28, N. Y.

VOL
4
195

VOL.
4
1956

Book Reviews

PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON THE PEACEFUL USES OF ATOMIC ENERGY; VOL. 10, RADIOACTIVE ISOTOPES AND NUCLEAR RADIATIONS IN MEDICINE, AND VOL. 11, BIOLOGICAL EFFECTS OF RADIATION; Editorial Board, Robert A. Charpie, Donald J. Dewar, André Finkelstein, John Gaunt, Jacob A. Goedkoop, Elwyn O. Hughes, Leonard F. Lamerton, Aleksandar Milojević, Clifford Mosbacher, César A. Sastre, and Brian E. Urquhart. Pp. ix plus 544 (Vol. 10) and ix plus 402 (Vol. 11); New York, 1956, United Nations. Price $8.00 per volume.

These volumes include all of the papers submitted to the Geneva Conference on the Peaceful Uses of Atomic Energy, held in Geneva, Switzerland, from Aug. 8 to 20, 1955, in the fields of medicine and radiobiology. The pertinent verbatim records of the Conference are also included.

Of the two volumes, volume 10 will probably hold the greater interest for the medical reader. Including as it does a series of papers in which are described some of the more significant work of many of the leading authorities in the field of radioisotope medicine throughout the world, Volume 10 gives an excellent cross section of the clinical and associated experimental applications of radioisotopes in medical science. The volume is divided into four sections: Isotopes in Medicine and Biology; Radioisotopes in Therapy; Radioisotopes in the Diagnosis and Study of Disease (Clinical Applications); and Radioisotopes in the Diagnosis and Study of Disease (Experimental Applications). In all four sections, most of the papers were written by workers living within the United States and the United Kingdom. There is, however, good representation of the work of investigators in many other parts of the world, including Russia.

The first section of Volume 10 is devoted to a series of four papers by Warren of the United States, McFarlane of the United Kingdom, Nakaidzumi of Japan, and Coursaget of France. These papers discuss, in a general way, the historical background of radioisotopes in each of the respective countries. The papers therefore serve as a background for the remaining papers given at the Geneva Conference.

The second section of Volume 10 presents, in a series of twenty-seven papers, a review of the work which has been done with radioisotopes in the field of radiation therapy. The scope of these papers ranges from descriptions of kilocurie teletherapy and multimegavolt radiation sources for the external application of ionizing radiation to descriptions of the internal use of radioisotopes in the treatment of principally malignant disease. In the latter category, several excellent papers appear on the subjects of the usefulness of radioactive colloids (Gold-198, Chromic Phosphate (P-32), Yttrium-90, and Lutecium-177) in the treatment of pleural and peritoneal effusions in malignant disease; the usefulness of radiophosphorus in the treatment of polycythemia vera; and the usefulness of radioiodine in the treatment of thyroid disease. Also included in this section is a number of sophisticated papers describing the neutron therapy of boron activated neoplasms of the brain, the irradiation hypophysectomy of individuals with 340-Mev protons and 190-Mev deuterons.

The third section of Volume 10, Radioisotopes in the Diagnosis and Study of Disease (Clinical Applications), is to this reviewer the most interesting portion of the volume. In it are included thirty-four papers, many of which are classical works describing the techniques, indications, and contraindications for a wide variety of radioisotopes in the study and diagnosis of clinical problems. Several papers discuss the problems concerned with the application of radioiodine in the diagnosis of thyroid disease. Another group of excellent manuscripts devotes attention to the problems of hematology which are amenable to study and solution by radioisotopic means. Brownell and Sweet describe their ingenious technique for the localization of intracranial and other lesions by

positron-emitting isotopes. The high resolution afforded by this method indicates that it will receive extensive application almost certainly in many medical diagnostic problems of the future.

In the fourth section of Volume 10 are included twenty additional papers concerned with the use of radioisotopes in the diagnosis and study of disease. Unlike the third section, however, most of these papers are devoted to experimental problems in medicine rather than to clinical application. As might be expected, these papers cover a wide variety of experimental problems, including the use of radiosodium and radiopotassium in electrolyte metabolism, the use of tritium-containing water in the same application, the use of radioisotopes in the study of tuberculosis, vitamin pathogenesis, muscle biochemistry, protein biosynthesis, and the modes of cancer induction. Three papers are also devoted to the use of radioisotopes in the study of public health problems.

Volume 11 is divided into four sections, with several of these further subdivided: Biological effects of Radiation; Modes of Radiation Injury and Radiation Hazards; Mechanism of Radiation Injury (Protection and Recovery); and Genetic Effects (Human Implications). The first section is a review of a rapidly-accumulating literature on the subject of the biologic effects of radiation. The papers appearing in this section should be quite useful to workers in this field, since many of them contain extensive bibliographies. This is particularly true of some of the foreign manuscripts.

The second section, on the modes of radiation injury and radiation hazards, is divided into three subsections, the first of which is concerned principally with radiation injury. Here, fourteen papers present extensive data on the early and late effects of radiation injury, injury due to radioactive fall-out, modes of acute radiation death, the effect of radiation dosage on the lifespan of the exposed individual, and the effects of chronic low intensity radiation exposure. The second subsection is devoted to the carcinogenesis and metabolism of bone-seeking isotopes and the final subdivision to a series of four papers on the effects of radiation on the reproductive system and on the fetus.

The third section of Volume 11 is devoted to a series of papers discussing the protection and recovery of biologic tissues and systems from radiation injury. As in the previous sections in this volume, and in Volume 10, the papers are accompanied by extensive bibliographies on the subject and give the reader an excellent background of information from which added study may be projected.

The final section of Volume 11 is devoted to a series of four papers on the genetic effects of radiation exposure. Although these papers do not resolve the many problems concerned with this highly controversial subject, they provide both the radiation worker and the physician alike with a superb discussion of the problems of genetic change induced by radiation.

In this book review, it is not possible to do more than outline a few of the high spots of the wealth of information and data presented at the International Congress of the Peaceful Uses of Atomic Energy, in Geneva in 1955. For the radiation worker, whether he be in the field of biology or medicine, these volumes are required reading. Although they are in no sense a pair of textbooks in the field of nuclear medicine, their breadth of coverage and their extensive bibliographies should prove invaluable to the physician who has only cursory contact from time to time with radioisotopes.

Russell H. Morgan, M.D.

SOCIO-ECONOMIC CONDITIONS AND TUBERCULOSIS PREVALENCE IN NEW YORK CITY, 1949-1951. By Anthony M. Lowell. New York Tuberculosis and Health Association, 1956. pp. 127. Abstracts available only on request to the New York Tuberculosis and Health Association, Inc., 386 Fourth Ave., New York 16, N. Y.

This well-documented study describes intensively in 42 pages of text and 85 pages of charts, illustrations, Health Area maps, and other statistical data "socio-economic conditions and tuberculosis prevalence in New York City."

The author's final conclusion is "The supporting evidence leads to the conclusion that where urban living is accompanied by inadequate or slum housing, low income, deleterious effects of overcrowding and poverty, tuberculosis continues to exist at a higher level of prevalence than where the general physical and social environment is salubrious. If optimum benefits are to be realized in mastering tuberculosis, progress in medicine and public health must be accompanied by comparable and parallel socio-economic improvements in living conditions."

Workers with long experience in the care of tuberculous patients are convinced that there are important interrelationships between psychological and emotional factors and the illness tuberculosis. It is conceded that these factors may not lend themselves to the same kind of precise statistical measurement as the more tangible characteristics used as indices in this study. However, the potentially significant adverse influence of the intangibles in the problem of tuberculosis merits systematic and vigorous search for acceptable methods of study which would make possible their inclusion in future community studies. Greater understanding of these elements in the total situation may hopefully further illuminate and materially alter the picture.

Ethel Cohen

VOL.
4
1956

MEDICAL RESEARCH: A MIDCENTURY SURVEY. Vol. I. American Medical Research in Principle and Practice. Vol. II. Unsolved Clinical Problems in Biological Perspective. Pp. (Vol. I) 765, (Vol. II) 740. Boston, 1955, Published for the American Foundation by Little, Brown & Company. Price (2 volumes) $15.00.

These two volumes on medical research represent a prodigious task, the (temporary) culmination of fifteen years of effort. They total 1,505 pages, printed on thin paper (not inclusive of 60 pages of introductory statements). There are no tables or text figures.

Volume I is entitled "American Medical Research in Principle and Practice," and includes four lengthy sections: (1) "Medical research in the perspective of biological, chemical, physical, and mathematical science"; (2) "Current trends and current problems in medical and biological research in the United States"; (3) "Research agencies"; (4) "Clearing results and controlling products of medical research"; and a brief appendix of major sources.

Volume II is devoted to "Unsolved Clinical Problems in Biological Perspective." The first chapter is entitled "Current metabolic concepts orienting research in biology and medicine"; the remaining nine chapters deal with selected specific conditions: cancer, infertility, arteriosclerosis, hypertension, the rheumatic syndromes, tuberculosis, the nature of viruses and virus diseases, alcoholism, and the biology of schizophrenia.

This reviewer finds the books puzzling in purpose, difficult to read (even aside from the physical fact of their length), and still more difficult to review.

The books are published for the American Foundation, established in 1924 by the late Edward Bok. Its present Chairman is the founder's son, Curtis Bok; the "Member in Charge" is Esther Everett Lape. These two volumes are presented jointly by the Foundation and a Committee of Consultants: 26 distinguished scientists (including 2 Nobel laureates), all of whose names are household words in American and world science. The committee includes physicians, biologists, chemists, physicists, and educators.

A first, and to this reviewer major, omission is the absence of exact definition of the identity of the persons who wrote the books. The authors are not named, either over-all, or as to individual sections or chapters. Presumably, from the title page, these authors were Miss Lape and her two associates, Eleanor M. Phillips and Margaret Thomas Edgar. The role of the Committee of Consultants was apparently confined to endorsement of the "central idea and the objectivity of the Foundation's performance (from the Foreword by Mr. Bok); and to "significant counsel" (from the "Introductory statements" by Miss Lape). The Foreword and the "Introductory statements" are the only portions of either volume for which authorship is specifically acknowledged. I have searched unsuccessfully for words indicating that the members of the Committee had read and critically reviewed the manuscripts of appropriate sections or chapters in their respective fields of special interest.

Not only is responsibility for authorship undefined (except by the implication that the authors were Miss Lape and her two associates); but also the reader is not provided with the degrees, academic backgrounds, and scientific qualifications of the writers; and is therefore unable to judge of their competence to undertake such highly complicated technical discussions, judgments as to the merits of the work of other investigators, etc., with which the pages abound. This lack of information renders still more regrettable the vague statements concerning the responsibility of the Committee of Consultants.

The purpose behind such a study as this is intimately entangled, at least in the mind of this reviewer, with the question as to the audience which the study is intended to reach.

As to purpose, Mr. Bok says in his Foreword: "Our effort has been to clarify such . . . problems as the role of . . . in the present report, research in biology, chemistry and physics in *relation to the maintenance of high standards of medical education and of medical care for the whole population.*"* It is this "central idea" which is endorsed by the Committee of Consultants. Says Miss Lape in her "Introductory outlining why and how this study was made": "The most urgent of present national needs in the medical field is thus conceived to be *expansion and improvement of medical education integrally related to research, and progressive improvement of medical practice.** . . . The medical research involved must be in biological perspective, utilizing the contributions of chemistry, physics, mathematics, and the results of research on atomic energy. This is the thesis of this study."

This is the forest. The trees are the pages devoted to "Illustrative presentation of the research of the various agencies in the first volume," i.e., universities, medical schools, research institutes, hospitals, industries, government, and other agencies; and "Illustrative presentation, in the second volume, of trends in basic research involved in solution of nine outstanding clinical problems."

This reviewer believes that the authors of these books have lost sight of the forest in detailed contemplation of the trees. Only portions of Volume I are devoted to the basic purpose outlined by Mr. Bok and Miss Lape. Section I consists of a lengthy (85 page) largely philosophic discussion of research. Sections 2 and 3 are especially pertinent to the issue, since they deal with such vital problems as "Conditions affecting basic research and . . . researchers," the financing of medical research, the evolving role of government, and a detailed (477 page) discussion of research agencies. Here, there is repeated emphasis on the too infrequently stressed facts that the successful prosecution of research requires brains; that brains require careful educational preparation in universities and medical school, and later, as they mature, tender nuturing in research agencies; that funds presently available for the support of research are perhaps already in excess of the supply of brains to use them wisely; and that research monies, especially for pet specific diseases and philanthropies, are certainly more readily to be had than funds to support the educational institutions and hospitals in which those who are to use them must be trained, and in which, moreover, most medical researchers must eventually work.

There is presented, in this respect, an enormous amount of information as to the relative sums available for research versus education; but, unfortunately, these data are textual, not tabular, and are widely scattered over many pages. To obtain a clear over-all picture, readily intelligible from a few tables and graphs, would require many weary hours of biostatistical analysis, which this reviewer was too fatigued to attempt, though the authors should not have been.

Volume II is the most remarkable achievement of the books, the more remarkable if, as is implied, Miss Lape and her lay collaborators were the authors. Each chapter is devoted to a description of what has so far been and what still remains to be accomplished in a series of 10 comparatively unrelated selected diseases or conditions. The discussions, purposely slanted from a fundamental biologic point of view, are excellent; and so well done that 10 experts, each of whom had devoted a lifetime to each of the 10 problems, could hardly have done better with individual chapters than the small unnamed group of presumably less technically trained authors have done with all ten. Previous reviewers of these books, some of them specialists in the knotty scientific problems discussed, have searched in vain for important omissions or errors, and are

*Italics mine.

VOL 4 195

glowing in praise of accuracy, clarity of analysis, and up-to-dateness. This reviewer, too, agrees on the excellence of these chapters. He reports the omission of a separate bibliography for each chapter, though the volume ends with 40 pages of alphabetically arranged "major sources," chosen primarily from the literature of the past fifteen years.

However, this reviewer does not believe that Volume II, dealing with the present status of research in and the unsolved problems of certain specific disease conditions, contributes significantly to the basic purpose of the entire study, as outlined above. The authors themselves recognize the evanescent character of such discussions. Miss Lape says: "Any current presentation of 'current trends' in biological and medical research must squarely face the realization that few trends, if they are lively, are 'current' for very long. The betatron and synchroton of today are likely to be the museum pieces of tomorrow."

These chapters of Volume II might perhaps better have been published as "Reviews" in the periodical scientific literature than in book form; certainly they would have been more widely read by interested investigators.

There remains the question of the unnamed audience to which these books are addressed. This is surely not to the lay public nor to the medical profession as a group. The method of approach is so highly technical as to be unintelligible to all except the most intimately concerned laymen; and the books are far too lengthy to appeal to most doctors. The major purpose of the study—"the expansion and improvement of medical education integrally related to research, and progressive improvement of medical practice"—is certainly a topic on which the laity *should* be widely informed, since at bottom the public is the source from which funds must come. Curious as it may seem, scientists too, and physicians, especially badly need similar information. But surely this is better accomplished than in a 1,500 page book by a series of short presentations in more widely disseminated media of lay information—the daily press, magazines, radio, television; and with the constant repetition necessary for the eventual salesmanship of even a good idea. The urgency for the support of education is propaganda, of course; but propaganda is effective with a mass audience only by constant reiteration over a fairly long period of time, by repeated small rapier thrusts rather than by a single massive attack.

Are the books addressed to medical investigators themselves? As for Volume I, hardly, since most of them are so concerned with their own urgent and intimate problems as to have no time for, and relatively small interest in, the voluminous discussions presented here. Those specifically concerned with the selected problems presented in Volume II will, however, find much to interest and stimulate.

One may perhaps assume that the desired audience is made up of administrators and trustees of educational institutions, research institutes, governmental agencies (including legislators), fund-raising bodies for particular research purposes (e.g., cancer, heart disease, arthritis, and a host of others), and of industry. For this group, Volume I is clearly pertinent; Volume II perhaps superfluous.

For whatever groups the books were written, it may be said that there is no doubt of the correctness of their substance, of the competence and honesty of the presentation, or of their potential value. That potentiality is, however, seriously impaired by the complete omission of any index. The reader who wishes precise information on any point is likely to be unable to find it. The lack of index lowers the value of the books as library reference works.

J. E. Moore

BIOFLAVONOIDS AND THE CAPILLARY. Edited by Roy Waldo Miner; Consulting Editor, Gustav J. Martin. By Gustav J. Martin and Albert Szent-Györgye (Conference Co-Chairmen), W. E. Baier, G. J. Boines, C. E. Brambel, W. Burroughs, E. W. Cheng, L. A. Fulton, D. Goebel, R. B. Greenblatt, C. T. Javert, R. E. Lee, F. Moewus, J. F. Rinehart, C. E. Story, L. Yoder, J. B. Youmans, and B. W. Zweifach. Pp. 99, with 30 illustrations. Ann. New York Acad. Sc. **61**: 637-736, 1955.

This small monograph, reporting a conference at the New York Academy of Medicine in February, 1955, concerns a subject of interest chiefly to persons actively working with bioflavonoids

because, as stated so succinctly by J. B. Youmans in a summary of the conference, "no satisfactory evidence of the effect of their (bioflavonoids) lack has been demonstrated. All of the five clinical papers . . . unfortunately . . . do not prove it (biological action in disease states) nor provide evidence of it."

The bioflavonoids include a large group of compounds, are widely distributed in nature often as yellow pigments, and have been used as the chief source of the natural yellow dyes. Citrus fruits are important dietary and pharmaceutical sources. Administration of these chemically active substances has led to several physiologic effects: enzyme inhibition, inhibition of epinephrine oxidation, potentiation of vitamin C, inhibition of induced increase in capillary permeability, some interference with anaphylactic shock, estrogenic activity in sheep grazing on clover containing an isoflavone, and a possible part in sexual activity of certain plants and lower forms. The bioflavonoids have not yet been found as normal constitutents of the animal body.

The monograph has many references, contains discussions of each paper, is well written and illustrated. B. W. Zweifach's article on, "Structural Make-up of Capillary Wall," should be of interest to persons in many fields. The booklet is very useful to anyone who wishes to study the bioflavonoids.

Frederick W. Barnes, Jr.

VOL. 4 195

DOCTOR AND PATIENT AND THE LAW. By Louis J. Regan, M.D., LL.B., Ed. 3. Pp. 716; indexed. St. Louis, 1956, The C. V. Mosby Company. Price $12.50.

The third edition of Dr. Regan's classical text on Medical Jurisprudence was completed just before his untimely demise in December, 1955. It represents an extensive rewriting and revision of the previous edition, bringing up to date the important judicial decisions in the various states which have altered previous concepts of the physician's responsibility in his relationships with his patients. The twenty-one chapters cover not only medicolegal problems arising between the physician and patient, but also hospitals, expert testimony, admissibility of evidence, and an excellent section on malpractice prophylaxis. There is competent discussion of operative permits, the important criminal laws affecting doctors, the present status of coroners and Medical Examiners, Federal Food, Drug, and Cosmetic Acts, and matters of confinement of insane persons. A section is devoted to the duties and liabilities of dentists analogous to those of physicians, and another to nurses and malpractice action.

The general format followed throughout the chapters is a presentation of basic definitions and problems with the use of extensive case citations to illustrate the various attitudes experienced in different Appeals Court decisions at the end of each section. The cited cases are referenced at the end and an excellent index makes the subject matter readily available. The text is written primarily for professional people in the practice of medicine and hospital administration but a great deal of it is of interest to laymen, to patients, and those who may become patients.

Dr. Regan's concept of the problem of malpractice is summarized in conclusions at the end of the text and is abundantly reflected throughout its entirety. His suggestions for alleviating the problem are worthy of quotation.

"There must be recognition of malpractice as a problem: that the conditions created by it are harmful to the physician and injurious to the public; and that action must be taken to counteract it. The public should be informed as to what constitutes malpractice and how really few cases of actual malpractice occur. The average medical man does not need to be urged to follow the dictates of good practice but it seems that he does have to be urged to take precautions to protect himself against malpractice claims. To be in a position to do so effectively requires a little study."

In this reviewer's opinion, every physician should take the self test on malpractice vulnerability included in Chapter 16 of this text and then study the remainder of the *Doctor and Patient and the Law* sufficiently to reassure himself that he can intelligently inform the public of the truth about malpractice actions as well as protect himself against unjust accusations.

Russell S. Fisher, M.D.

THE HISTORY OF THE THERAPY OF TUBERCULOSIS AND THE CASE OF FREDERICK CHOPIN. By Esmond R. Long, M.D. Pp. 71; indexed. Lawrence, Kan. 1956, University of Kansas Press. Price $2.00.

The brief period of Chopin's life spent with George Sand and her children on the island of Mallorca has had an understandable fascination for many who have concerned themselves with the history of the great Polish composer-pianist. A visit by Dr. Long to Valdemosa, the sight of the Mallorcan monastery where Chopin and Sand lived, was apparently responsible for a particularly happy notion—to retell briefly Chopin's life story (with particular accent on his long and losing struggle against tuberculosis) as background material for the second half of the book, a history of the therapy of tuberculosis. Chopin's illness illustrates dramatically the poverty of medical knowledge about tuberculosis—its epidemiology, pathology, diagnosis, and therapy—a short century ago. Dr. Long reminds us that "in 1835 hemoptysis was not yet considered a pathognomonic sign of tuberculosis, but rather a possible forerunner of the disease and indeed a frequent cause of it." The author speculates on how many young people Chopin, coughing steadily while he taught, might have infected. Some lively figures cross the stage, albeit briefly, in his book: Cherubini (who died of tuberculosis in 1841); Hahnemann and the homeopathic school so prominent in Paris at that time; Andral (who undertook controlled studies which failed to disclose any benefits from homeopathic remedies); the charlatan Koreff with his "magnetic" cures; the celebrated orthodox Broussais school, with its reliance on copious bleeding and semi-starvation to relieve inflammation; the leading phthisiologist in London, Sir James Clark, who pooh-poohed the idea that consumption was contagious; and the great French authority, Pierre Charles Alexandre Louis, a therapeutic nihilist at a time when nihilism was by far the soundest position. Louis pointed out that it was fortunate for Chopin that he fell into the hands of the homeopaths early in his illness, since at least they omitted the prevalent, rigorous therapy of bleeding, emesis, etc., which would probably have shortened Chopin's life. Chopin's medical career ends on a suitably dramatic note: the great French pathologist Cruveilhier performs a partial necropsy, removes Chopin's heart, which Chopin requested to have sent back to his native Poland, and then leaves no written record of the necropsy. Why (asks Dr. Long) did "this greatest of living pathologists, noted for the accuracy of his observations, [leave] no written record?"

The second half of the book is of interest primarily as an excellent reminder of the useless and, at times, harmful "remedies" which can develop over the centuries when one is dealing with a disease for which there has been (until recently) no really effective treatment. Perusing the history of tuberculous therapy and considering the antibiotics available today, one wonders how much place there remains for some of the nonspecific measures still in use, for example, bed rest.

Louis Lasagna

FIFTH ANNUAL REPORT ON STRESS—1955-1956. Edited by Hans Selye, M.D., Ph.D., D.Sc. (Hon.), F.R.S. (Canada), F.I.C.S. (Hon.), and Gunnar Heuser, M.D. Pp. 815, with 49 figures; indexed. New York, N. Y., 1956, M.D. Publications, Inc. Price $20.00.

The evolution of the concepts of stress, stressors, and diseases of adaptation has been accompanied by considerable confusion and misinterpretation in the past six years. The ramifications and potential implications of this doctrine have become so comprehensive that virtually all areas of medicine have been encompassed, and considerable interest and discussion have been aroused.

The present volume is undoubtedly the best of the series to date. It subserves the initial functions formulated in 1951 of "a guide to the entire literature on stress" and "of a critical correlation of pertinent facts," and, in addition, provides a medium for authoritative and critical reviews by other responsibile investigators. This amplifies the scope of the presentation and potentially gives it a balance which otherwise would be, and heretofore has been, lacking. The critique by Dwight J. Ingle, entitled "The Role of the Adrenal Cortex in the Etiology of Disease" emphasizes this point. It is a stimulating discussion which serves further to demonstrate that given the same or essentially similar experimental results, two widely different theories may emerge. In essence, this is one of the most valuable areas of Selye's contributions, that the heu-

ristic merit of his experiments and theories has been of such caliber as to stimulate, if not to provoke, the essay mentioned above, as well as other less erudite analyses of methodology.

There are a variety of other current topics covered by leading investigators in pituitary-adrenal physiology. These include a discussion of primary aldosteronism by J. W. Conn, a review of neurosecretion by Ernst Scharrer, an analysis of adrenal influences on the stomach by Seymour J. Gray and co-workers, and an important presentation of original work by U. S. Von Euler on the elaboration of catechol hormones under conditions of stress. There are also reviews by Don Nelson on adrenocortical secretion, by T. F. Dougherty and R. D. Higginbotham on inflammation and detoxification, and by H. C. Stoerk on the effects of cortisone on lymphoid tissue and immunity. The remaining article by R. A. Spitz entitled "Some Observations on Psychiatric Stress in Infancy" seems somewhat out of place with respect to the significance of its message and its limited appeal. The author's attempt to correlate the "emotional deprivation syndrome" of Spitz with Selye's general adaptation syndrome by pointing out that in the former there is "absence of autoerotic activity" and in the latter there exists "subnormal libido," falls short even of being specious, in the opinion of this reviewer.

The major appeal of this volume will be to investigators in the field of endocrinology, but there is much to recommend it from the standpoint of the internist and even the general practitioner. Over 6,000 references cover the latest information on all aspects of stress research and adrenal cortical therapy. In addition, there is provided a comprehensive correlation of recent developments in these fields in a topically arranged fashion.

Paul J. Rosch

VOL 4 195

OL.
4
956